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LONG TERM PREVENTION OF TOOTH DECAY AMONG DIABETIC CHILDREN

JULIAN D. BOYD, M.D.

IOWA CITY

Earlier reports from this institution have described the lessening of dental caries observable in children whose diets have been supervised because of metabolic or digestive disorder.[1] Recently, the data have been reviewed so as to permit statistical evaluation. This report is one of a series based on the review. It is designed to cover only limited aspects of the problem and is supplemented by other reports already published or in preparation. The studies were made between the years 1926 and 1937, while Charles L. Drain, D.D.S.,[2] then professor of pedodontics and director of the children's dental clinic in the hospital, and I were collaborating jointly. The largest group of children studied comprised those who were under supervision because of diabetes mellitus. Over 200 such children were observed for various lengths of time during the designated period of years. Because of the recognition of the error inherent in short periods of observation, statistical consideration has been restricted to data for children who were observed recurrently for not less than three years each.

The first individualized statistical analysis of dental data relating to these diabetic children[3] was restricted further to include only those who had been observed for forty months or longer following the shedding of all carious deciduous teeth. In relevant publications and in earlier reports[4] data were presented to establish the validity of the following conclusions:

1. The average incidence and rate of progression of caries in 55 teen-age diabetic children was far less than in the average child population of similar age. Comparisons have been based on the reports of others elsewhere for supposedly normal school children as well as for children studied regionally both among the school population[5] and among children observed medically for long periods of time because of syphilis who did not follow any prescribed dietary regimen.[4]

2. The number of permanent tooth surfaces already affected by caries at the completion of shedding of deciduous teeth not only was distinctly lower than the so-called "normal" average but was inversely proportional to the duration of

From the Departments of Pediatrics and Pedodontics, Colleges of Medicine and of Dentistry, State University of Iowa.

1. Boyd, J. D., and Drain, C. L.: The Arrest of Dental Caries in Childhood, J. A. M. A. **90**:1867 (June 9) 1928. Boyd, J. D.; Drain, C. L., and Nelson, M.: Dietary Control of Dental Caries, Am. J. Dis. Child. **38**:721 (Oct.) 1929.

2. Dr. Drain died on June 5, 1937.

3. Boyd, J. D.: Nutrition as It Affects Tooth Decay, J. Am. Dietet. A. **18**:211 (April) 1942; Prevention of Dental Caries in Late Childhood and Adolescence, J. Am. Dent. A. **30**:670 (May) 1943.

4. Boyd, J. D.: The Role of Diet in the Control of Dentinal Caries, J. Am. Dent. A. **27**:750 (May) 1940.

5. Brauer, J. C.: Unpublished data.

the diabetic regimen prior to that time. The correlation coefficient was of such magnitude that it precluded chance as an explanation.

3. The extent and the rate of advance of caries in these children's teeth bore a reciprocal relationship to the level of fluoride content of the domestic water supply for each child, but the level of correlation was so low that the validity of the association could not be established.

In another study [6] the same data were reviewed further to offer evidence (1) that dental enamel was protected from the initiation or the extension of caries in a manner comparable to that observed in dentin and (2) that the observed protective effect could not be attributed to the filling of cavities or to other dental care of the teeth, in view of the fact that the policy followed was

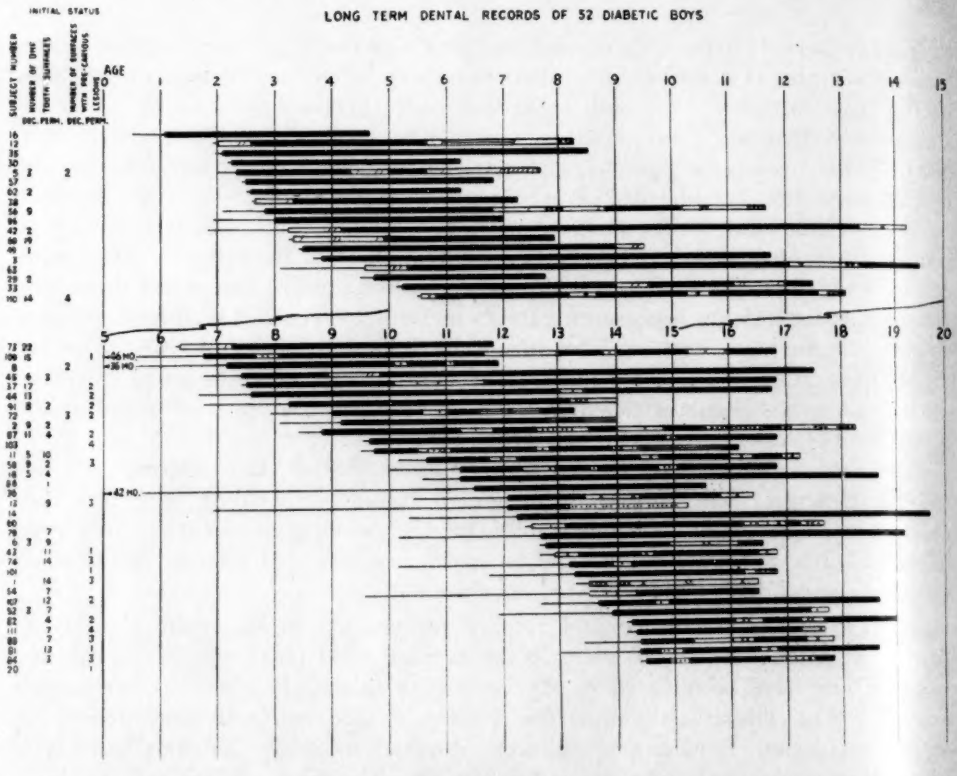
LONG TERM DENTAL RECORDS OF 52 DIABETIC BOYS
INITIAL STATUS
SUBJECT NUMBER
NUMBER OF DMF TOOTH SURFACES
NUMBER OF SURFACES WITH PRE-CARIOUS LESIONS
DEC. PERM.
DEC. DEC.
AGE
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
36 MO.
36 MO.
42 MO.

Chart 1.—Individual records of progressive dental status of 52 boys with diabetes mellitus. Length of each bar indicates duration of intermittent dental observation; solid black areas indicate periods of freedom from new dental lesions; unshaded areas contain symbols to indicate number of tooth surfaces with new lesions which appeared during the corresponding interval. Symbols have meanings as follows: diagonal line, one DMF deciduous tooth surface; crossed diagonal lines, one DMF permanent tooth surface; dot, one surface with a pre-carious lesion apparently limited to the enamel (preponderantly developmental pits and fissures appearing coincident with the eruption of the tooth). Intervals of prolonged non-observation are indicated by a horizontal line through the bar. The duration of diabetes mellitus prior to the initial dental examination is indicated by the length of the single horizontal line to the left of each bar graph. DMF signifies decayed, missing or filled (see text).

to leave all cavities unfilled or untreated, unless their size or position interfered notably with mastication. Such unfilled cavities showed no greater trend toward

6. Boyd, J. D.: Dietary Control of Enamel Caries, J. Am. Dent. A., to be published.

extension of caries than did noncarious areas, so long as the dietary regimen was observed. In an earlier study, already cited,[4] comparison was made between the caries experience of diabetic children and that of children with hereditary syphilis who received dental supervision of similar frequency and type. There was no evidence that the dental observation and prophylactic care had led to any noteworthy lessening of the attack rate of caries in the children with syphilis. Therefore, there is no reason to ascribe the low rate of caries attack in the diabetic children to the dental care in itself or to any other local measure. All evidence thus far advanced favors the conclusion expressed in the earlier reports based on clinical impressions, namely, that caries did not appear or extend during the continuance of the prescribed dietary regimen.[1]

In contrast with the limited subject clientele of the earlier statistical studies, the current study includes the data relating to all diabetic children who had been observed recurrently for three years or longer. It permits consideration of 111 children, 52 boys and 59 girls. The average duration of observation (sixty-seven

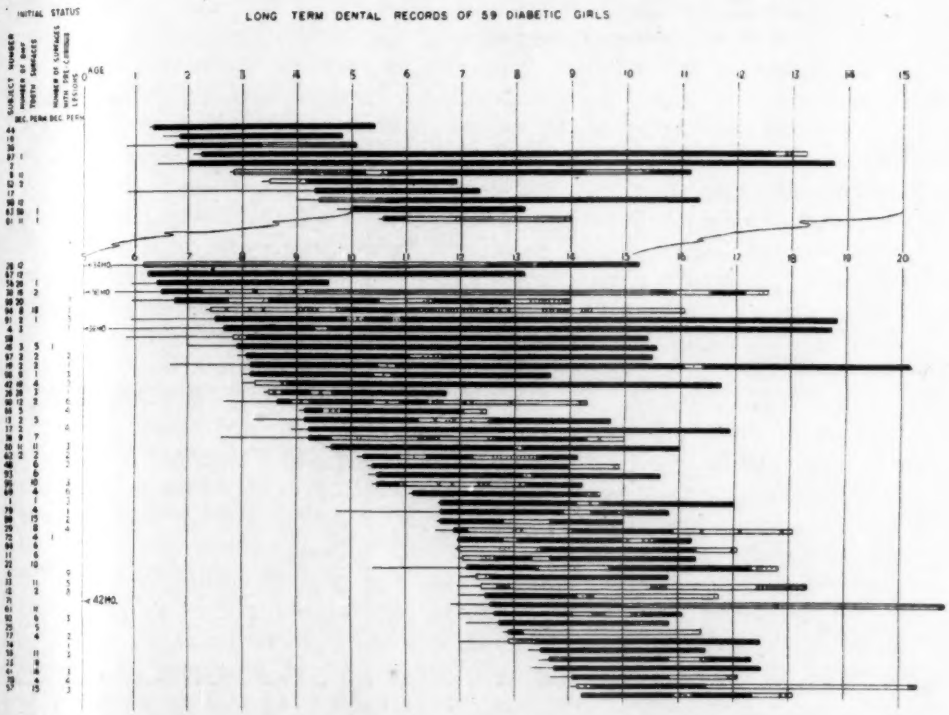

Chart 2.—Individual records of progressive dental status of 59 girls with diabetes mellitus. The meaning of the symbols is the same as in chart 1.

and one-half months) for each sex group exceeded five and one-half years; the range was from thirty-six to one hundred and forty-four months. The age of subjects at the time of initial observation ranged from 14 months to 14 years, with an essentially uniform frequency distribution between these extremes. The record of each subject is summarized diagrammatically in charts 1 and 2, for boys and girls respectively. The diagram for each child indicates the chronologic factors relating to the dental record, the age at which diet modification because of diabetes became necessary, the initial extent of dental lesions in deciduous and

permanent teeth and the number and time of appearance of subsequent dental lesions. Values are expressed in terms of the number of tooth surfaces affected. Distinction is made between lesions which may be termed pre-carious and those presenting presumptive or definite evidence of decay. The pre-carious lesions comprise primarily pits and fissures, and most of them appeared coincidentally

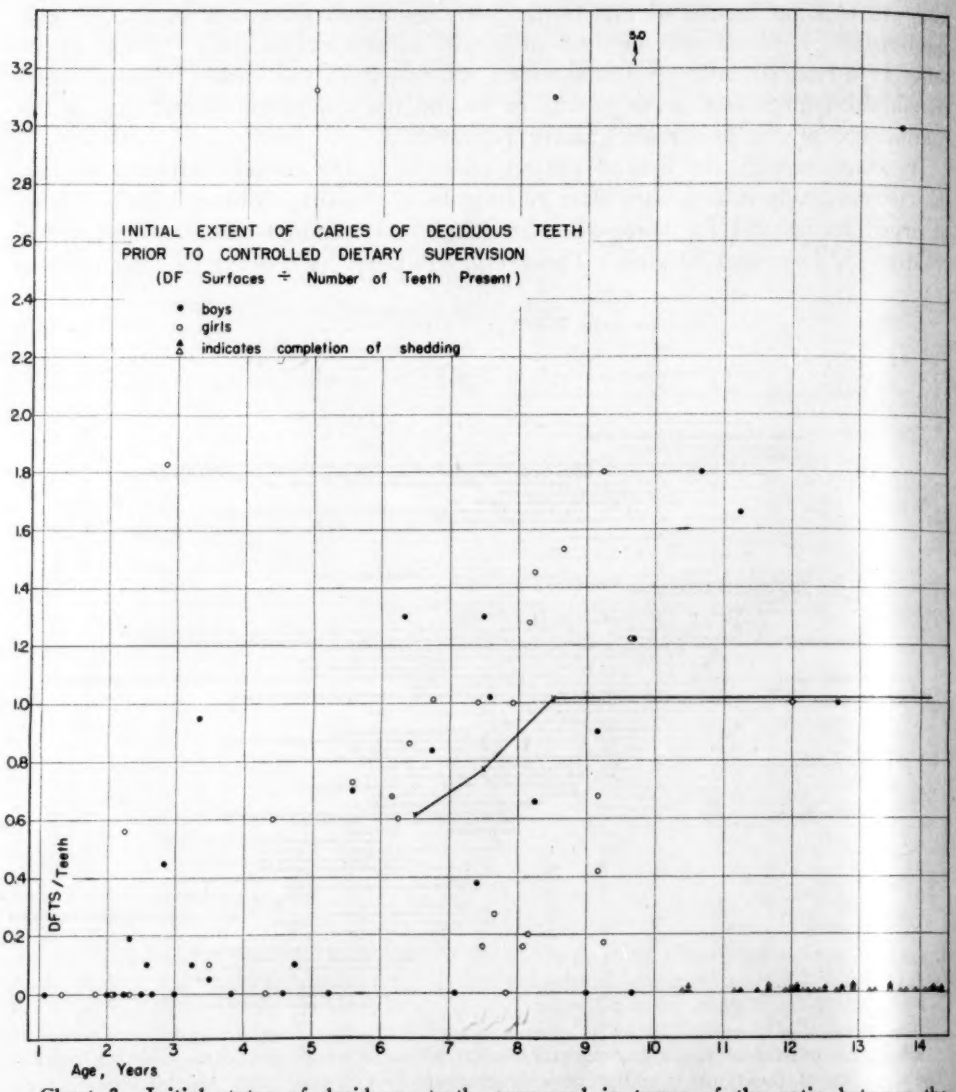

Chart 3.—Initial status of deciduous teeth, expressed in terms of the ratio between the number of decayed or filled (DF) tooth surfaces and the number of deciduous teeth present in the mouth concurrently. The reference line is calculated from the Hagerstown study.

with the eruption of teeth. Some such lesions became apparent in the dental records months or years after the tooth had erupted and probably represent areas of enamel caries. In the aggregate these lesions do not contribute a great deal to the score of acquired lesions and are not included as areas of decay in the calculated increment rates. Special consideration has been given to them in another publication.[6] Areas indicated as carious include open cavities, fillings and

decayed teeth lost through extraction. Extracted teeth were assumed to have had the equivalent of three carious surfaces. Hereafter in the text and in the tables, the decayed, missing or filled tooth surfaces are referred to as DMF, in accordance with standard nomenclature.[7]

The extent of caries at the time of the initial examination is portrayed further in charts 3 and 4: Chart 3 deals with deciduous and chart 4 with permanent teeth. In chart 3 values are expressed in terms of the ratio between the number of deciduous tooth surfaces showing caries or fillings and the total number of deciduous teeth present in the mouth. Chart 3 includes also the evidence available as to the age at completion of shedding of all deciduous teeth of the subjects who were seen first during late childhood. Chart 4 is expressed in terms of the actual number of decayed, missing or filled tooth surfaces versus the age for each child. For purposes of comparison, the values reported from studies of Klein and his colleagues [7] on pupils of the elementary schools of Hagerstown, Md. have been indicated on the charts.[8]

Chart 5 expresses graphically the extent of decay in permanent teeth at the terminal observation for each subject. For comparison, the corresponding average values from the Hagerstown study [9] are included.[10]

Table 1 presents the average increment rate for the appearance of newly carious tooth surfaces for each child included in the study. The values are expressed in terms of the average number of newly carious, missing or filled tooth surfaces per annum. Separate consideration is given to girls and to boys. All lesions of enamel or of dentin were listed as carious, with the exception of noncarious pits and fissures. All extractions performed during the course of study have been listed as their equivalent number of DMF surfaces, with the exception of six teeth which were noncarious at the time of their removal. One of these teeth was lost because of trauma; the other five were from the mouth of a boy who had severe periodontoclasia at the time of his first examination (subject 14 y). Many of the lesions listed as carious were of minimal extent and did not progress in area after their initial discovery.

Table 1 also lists the duration of observed nonadvance of caries for each subject. In some, the whole period of nonadvance was consecutive; in others, periods of nonadvance were interspersed with periods during which new areas of decay made their appearance. The longest period of uninterrupted nonadvance for each child is listed in column 3 of table 1. Column 4 represents the aggregate duration of significantly long periods of nonadvance, expressed in terms of the proportion of each subject's total period of observation which was free from advancing caries. Periods of less than twelve months' nonadvance have been disregarded in column 4, because of the possibility that during short intervals the latency of caries may have obscured the true rate of advance.

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7. Klein, H.; Palmer, C. E., and Knutson, J. W.: Studies in Dental Caries: I. Dental Status and Dental Needs of Elementary School Children, Pub. Health Rep. **53**:751 (May 13) 1938.

8. Values for deciduous teeth were calculated from tables 1, 5 and 7 of Klein's report of 1938.[7] Values for permanent teeth were calculated from table 9. Whereas question might arise as to the propriety of making comparison between the caries progress in the diabetic children and in the children from the Hagerstown study, unpublished data [5] indicate close parallelism between the extent of caries of the Hagerstown children and that of Iowa children of corresponding age seen in the University dental clinic. The relation between the averages is illustrated in diagrams appearing elsewhere.[5]

9. Klein, H., and Palmer, C. E.: Studies in Dental Caries: IX. The Prevalence and Incidence of Dental Caries Experience, . . . in High School Children, Pub. Health Rep. **55**:1258 (July 12) 1940.

10. The broken lines are from Klein's [7] table 9. The straight line is from figure 1 of his report of 1940.[9]

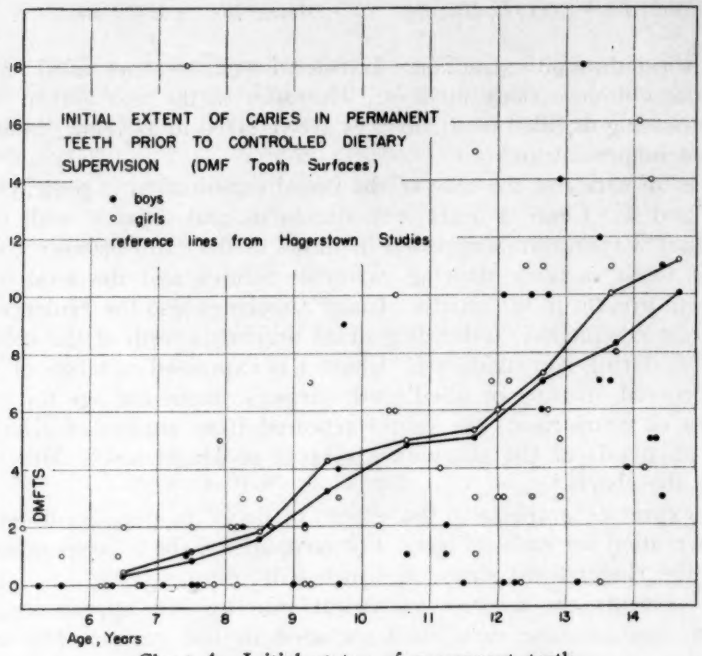
INITIAL EXTENT OF CARIES IN PERMANENT TEETH PRIOR TO CONTROLLED DIETARY SUPERVISION (DMF Tooth Surfaces)
• boys
○ girls
reference lines from Hagerstown Studies
DMFTS
Age, Years

Chart 4.—Initial status of permanent teeth.

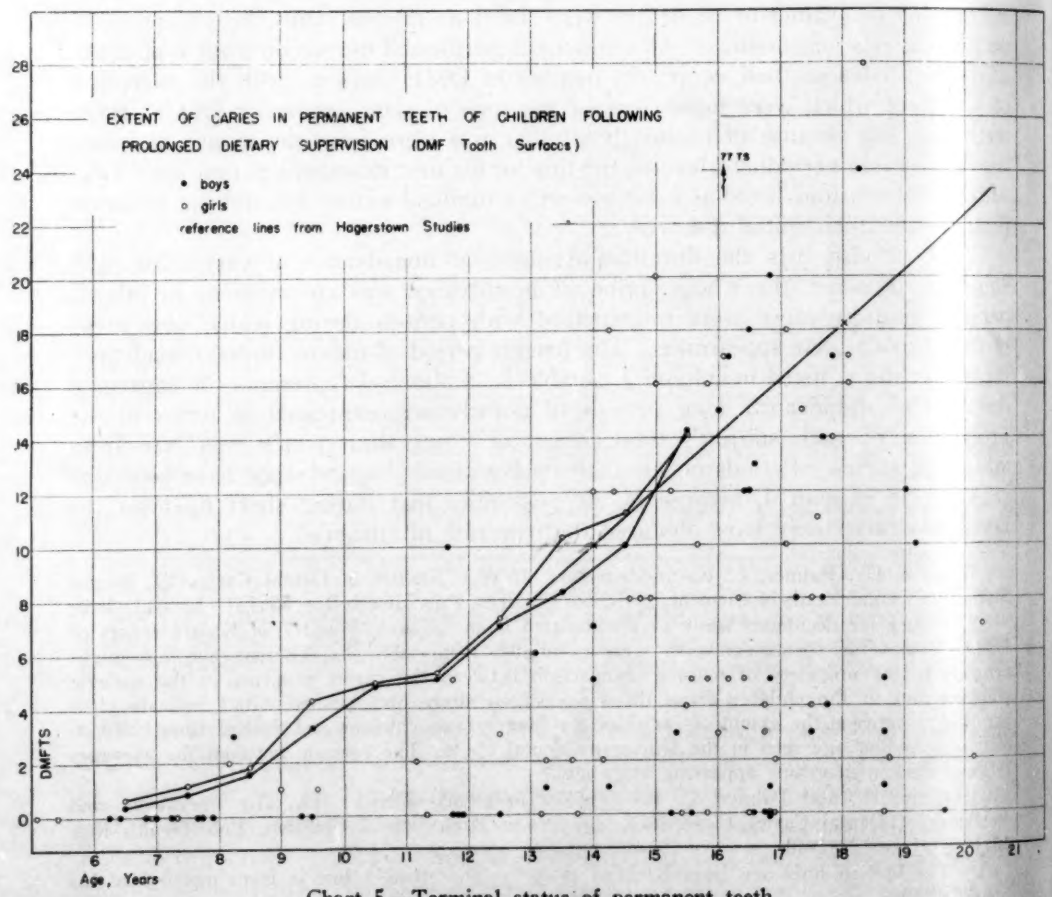
EXTENT OF CARIES IN PERMANENT TEETH OF CHILDREN FOLLOWING PROLONGED DIETARY SUPERVISION (DMF Tooth Surfaces)
• boys
○ girls
reference lines from Hagerstown Studies
DMFTS
Age, Years

Chart 5.—Terminal status of permanent teeth.

TABLE 1.—*Rate of Advance of Caries and Duration of Freedom from New Carious Lesions: Individual Summaries of Records*

Boys					Girls				
	Rate of Increment, Tooth Surfaces per Annum		Duration of Nonadvance			Rate of Increment, Tooth Surfaces per Annum		Duration of Nonadvance	
Subject No.	DMF *	Pre-carious ‡	Consecutive, Mo.	Aggregate, per Cent of Total Observation	Subject No.	DMF *	Pre-carious ‡	Consecutive, Mo.	Aggregate, per Cent of Total Observation
3y	0	....	95	100	2x	0	....	141	100
60y	0	....	89	100	37x	0	....	92	100
86y	0	....	89	100	45x	0	....	92	100
6y	0	....	78	100	67x	0	....	83	100
35y	0	....	77	100	44x	0	....	49	100
57y	0	....	52	100	23x	0	....	45	100
36y	0	....	49	100	56x	0	....	38	100
30y	0	....	48	100	63x	0	....	37	100
96y	0	....	48	100	10x	0	....	36	100
62y	0	....	44	100	17x	0	....	36	100
16y	0	....	43	100	74x	0	....	36	100
29y	0	....	36	100	60x	0	0.16	76	100†
44y	0	0.11	110	100†	6x	0	0.29	42	100†
103y	0	0.14	86	100†	25x	0	0.57	42	100†
92y	0	0.20	60	100†	62x	0	2.81	47	100†
37y	0	0.21	112	100†	19x	0.08	0.08	112	96†
82y	0	0.26	46	100†	91x	0.09	0.44	103	97†
101y	0	0.29	41	100†	71x	0.12	....	50+	?
88y	0	0.30	40	100†	42x	0.12	....	95	96
8y	0	0.42	57	100†	4x	0.18	....	111	99
100y	0	0.60	121	100†	96x	0.18	....	35	94
107y	0	0.66	36	100†	87x	0.18	....	125	95
14y	0	2.20	38	100§	1x	0.19	....	30	92
73y	0.18	....	55	83	58x	0.26	....	88	98
18y	0.18	0.72	47	70	97x	0.27	0.27	46	92
45y	0.20	....	92	91	52x	0.29	....	33	81
38y	0.22	....	47	86	13x	0.36	0.72	26	90
72y	0.24	0.24	31	61†	48x	0.44	....	28	78
84y	0.24	0.72	25	92†	12x	0.47	0.47	27	75
42y	0.27	....	110	83	78x	0.49	....	25+	?
20y	0.30	2.10	26	65†	98x	0.58	....	68	82
49y	0.33	....	66	92	81x	0.59	....	5	?
74y	0.51	0.25	26	74	89x	0.60	....	16	75
91y	0.52	....	59	85	26x	0.62	....	25	64
43y	0.52	....	26	56	41x	0.66	....	21	58
63y	0.60	....	81	80	22x	0.71	0.71	31	68
58y	0.61	0.15	26	68	79x	0.72	....	27	54
13y	0.69	....	17	63	93x	0.77	0.19	39	95†
33y	0.69	....	45	72	77x	0.88	....	49	89
79y	0.77	0.58	45	72†	65x	0.90	....	27	67
111y	0.84	....	22	67	30x	0.90	0.27	9	?
69y	0.87	....	36	65	11x	0.94	....	32	63
110y	0.93	....	28	78	72x	0.94	....	23	45
2y	1.08	0.83	31	53	84x	0.99	....	34	56
12y	1.12	....	36	48	57x	1.04	....	20	72
81y	1.17	....	11	..	55x	1.09	....	23	52
56y	1.24	....	48	55	69x	1.17	....	37	90
11y	1.24	0.62	17	22	29x	1.30	....	22	30
1y	1.40	....	36	84	28x	1.32	....	22	?
87y	2.12	0.96	51	72	38x	1.57	0.35	20	29
5y	2.44	....	24	38	61x	1.76	....	17	41
54y	3.67	....	..	..	90x	1.76	....	14	21
					99x	1.79	0.28	24	63
					95x	2.13	....	12	27
					9x	2.88	....	43	43
					33x	3.05	....	0	?
					92x	3.33	....	29	80
					94x	6.45	....	13	12
					36x	8.90	....	19	48

* DMF signifies decayed, missing or filled; see text.

‡ Pre-carious refers to clinically significant pits or fissures or other irregularity of enamel. Most of the increment of pre-carious surfaces can be accounted for through eruption of additional teeth during course of study.

† Pre-carious lesions are not included.

§ This boy lost five noncarious teeth; see text.

The summary of the results for the whole series of subjects is offered in table 2.

COMMENT

This review has been made to demonstrate the degree in which the regular ingestion of an adequate diet, as exemplified by the diet prescribed in this institution for diabetic children, will serve to prevent the development of caries. If such a diet can protect teeth from decay, one would expect no further caries in a child who ingests and utilizes regularly a diet as it is prescribed. If, however, further caries develops in a diabetic child while he is ostensibly following such

TABLE 2.—*Rate of Advance of Caries and Duration of Freedom from New Carious Lesions: General Summaries of Records*

	Rate of Increment, DMFTS * per Annum	Duration of Nonadvance	
A. Average response		Consecutive, Months	Aggregate, per Cent of Total Observation
Boys			
Mode	0.00	..	100
Median	0.21	45	86
Mean	0.47	52	80
Girls			
Mode	0.00	..	100
Median	0.47	34	90
Mean	0.92	44	77
Total subjects			
Mode	0.00	..	100
Median	0.29	42	86
Mean	0.71	47	78
B. Frequency distribution		Number of Subjects	Per Cent of Total
Rate of increment, DMFTS * per year			
0.00		38	34
0.20 or less		49	44
0.40 or less		59	53
0.70 or less		74	67
1.00 or less		87	78
1.50 or less		98	88
2.00 or less		102	92
More than 2.00		9	8
Aggregate duration of nonadvance, months			
108 or more		8	7
72 or more		23	21
48 or more		37	33
36 or more		66	60
18 or more		99	89
15 or less		8	7
Aggregate duration of nonadvance, per cent of total period of observaton			
100		38	34
90 or more		52	47
75 or more		65	59
50 or more		91	82

* DMFTS signifies decayed, missing or filled tooth surfaces.

a diet, one might expect to demonstrate that the child had not adhered to the diet as prescribed. These assumptions are supported by the data at hand.

The principles of dietary prescription employed routinely in the treatment of diabetic children included in this study have remained constant throughout the interval under consideration. They have been designed to meet fully all nutritional needs. Foods have been prescribed specifically both as to nature and as to quantity, determined by weight or measurement of each ingredient. Basically the menus have included more liberal amounts of milk, eggs, meat, vegetables and fruits than most children receive. Each child was asked to take a teaspoon of cod liver oil daily, regardless of age or season. Revision of prescribed diets was made often enough to keep pace with advancing needs. Sugar as such has not been prescribed but has been present at all times as a natural constituent of foodstuffs. A review of the amounts of specific protective factors which the pre-

scribed diets supplied reveals that such supplies equaled or exceeded recent estimates as to needs. Prior to the year 1933, diets high in fat were employed routinely; thereafter, the proportions of calories derived from fats and from carbohydrates have corresponded closely with current recommendations for the nutrition of normal children. No difference of dental response was discernible for the one regimen as compared with the other; both served to safeguard against caries.[11] The nature of the diets employed has been discussed elsewhere.[12]

The average child in this series and the great majority of individual subjects showed much less advance of caries than would be expected for the general population. In 34 per cent of the children, caries was checked completely throughout the whole period of observation, and in 89 per cent of the group there was no advance for at least eighteen months.

On the basis of the Hagerstown studies, an average increment of approximately 2 new DMF surfaces per annum was predicted for the average teen-age child. In the Iowa study, by contrast, 92 per cent of the children had values less than that number; 88 per cent had less than 1.5 new DMF surfaces per annum. The average for the whole group was less than half that value; the median value was only 0.29. Moreover, a relatively small group of subjects contributed preponderantly to the total incidence of new carious surfaces. To permit appraisal of the regularity of ingestion of the prescribed diet by those whose performance deviated most strikingly from the median performance, 18 children have been chosen for individual notice. These 18 include the following groups: (1) the 13 children whose annual increment of caries exceeded 1.5 DMF surfaces per annum; (2) the children whose increment was greater than the average and who had less than eighteen months' freedom from advancing caries (all but 2 of these are included also in the first group); (3) 3 children whose increase in precarious lesions of the enamel was outstanding during the period of study. The information concerning these 18 nonconformists is assembled in table 3.

The personal and environmental factors recorded in table 3 are of such nature and degree that they could prevent the maintenance of a strictly prescribed regimen by a patient who visited the clinic only periodically for appraisal. Examinations and interviews at the clinic did not always elicit immediate evidence that home management was not in accordance with the prescribed standard; social records and observations made during field visits to the patients' homes often were of greater value. Certain patients or their parents admitted freely that they had not followed the advice as to diet, either specifically or in general. Economic factors probably stood highest in interfering with the use of the prescribed regimen. The cost of care for a diabetic child was considerable; the diet prescribed cost more than the sum expended normally for food for a child by families in limited circumstances. Almost without exception, the patients in the series were medically indigent, their hospital and medical fees being paid through state subsidy. Usually it was necessary to enlist state aid to assure the supply of necessary foodstuffs and of insulin. Various communities differed in their readiness to provide supplies and also in their regularity of supply. Families moving to new localities usually found it difficult, sometimes impossible, to reestablish the relief arrangement they had been accustomed to previously. One should wonder less that some children failed to maintain their regimen than that so many were able to do so creditably. Some of the

11. Boyd, J. D.: Unpublished data.

12. Boyd, J. D.: The Use of Standard Diet Formulas in the Control of Juvenile Diabetes Mellitus, J. A. M. A. **87:** 1020 (Sept. 25) 1926; Diabetes Mellitus, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1942, vol. 3, chap. 12.

TABLE 3.—*Individual Analysis of Children Showing Poorest Control of Dental Caries While Presumably Under Dietary Supervision*

	Recognized Personal and Environmental Factors Interfering with Prescribed Dietary Regimen																						
	Economic				Social										Personal				Medical				
Subject Number	Medical Indigency	Economic Inadequacy	Chronic Unemployment	Uncooperative Local Relief Agencies	Broken Home	Mother Out of Home or Dead	Mother or Father Invalid	Drunkenness of Parent	Interfering Relatives	Home Socially Unfit	Unhappy Home	Delinquency of Child	Child Fully Responsible for Own Care	Child Living Out of Home	Noncooperative Parents	Noncooperative Child	Cooperation Inconstant	Admitted Dietary Nonconformance	Prolonged Absence from Clinic	Neglect of Diabetic Control	History of Diabetic Emergencies	Other Concurrent Illnesses	Dental Abnormalities Other Than Caries	Comments
36x	+	..	..	..	..	..	+	..	..	..	..	..	..	..	+	+	+	..	+	+	..	+	..	Had congenital dislocation of hips; was in double hip spica for about half of observation period; was absent from clinic for more than eighteen months; caries advanced during that interval
94x	+	+	+	+	..	..	+	..	..	+	..	..	..	..	+	+	..	+	..	+	+	..	..	Sister of number 95x; economic status and familial indifference made control of diet and of diabetes impossible
54y	+	..	..	..	..	..	+	..	..	..	..	+	+	+	+	+	..	+	..	+	..	..	..	Boy had sole responsibility for his own care; failed to follow the prescribed routine, became delinquent and was committed to a state institution
92x	+	+	+	..	..	..	..	+	..	+	..	..	..	..	+	..	..	+	..	+	+	..	..	Attempted to cooperate, but socioeconomic factors made adequate care for her condition impossible
33x	+	..	..	+	..	+	+	..	+	+	+	+	+	..	+	+	..	+	+	+	+	..	..	At twelfth year had sole home responsibility for her senile father and four grown brothers; neither they nor she gave her care any consideration
9x	+	..	..	..	+	..	+	+	+	..	..	..	..	..	..	..	+	+	+	+	+	..	..	Prescribed regimen was ignored for first twenty-five months; during that time 22 new cavities developed; with no attention to cavities but with firm establishment of regimen caries ceased abruptly; see chart 1.
5y	+	..	..	+	..	..	..	..	..	..	..	..	..	..	+	+	+	..	+	+	..	..	..	Mother attempted to follow regimen for two years, then abandoned it; during following two years nine new cavities developed

95x	+	+	+	+	..	..	+	..	..	+	..	..	..	..	+	+	..	+	..	+	+	..	..	Sister of number 94x; diabetes was not controlled adequately at any time while she was at home; prescribed diet was not observed; died subsequent to this study owing to diabetic complications
87y	+	..	..	..	..	..	..	..	..	..	..	..	..	..	+	+	+	+	+	..	..	..	..	Note prolonged freedom from decay, then rapid advance of caries following admitted relaxation of dietary control and adoption of his family's dietary practices
99x	+	..	..	..	..	+	..	..	+	..	+	..	+	..	+	+	+	+	..	+	..	..	..	Home physician, also a diabetic patient, discouraged attmpts to treat this girl; patient had full responsibility for her own care and for maintaining the home; mother worked full time out of home
90x	+	..	..	..	..	..	+	..	+	..	+	..	..	..	..	+	+	..	..	+	..	..	..	Home resources adequate, but senile parental relatives living in home interfered continually with child's activities; girl became rebellious and refused to cooperate in her care
61x	+	+	+	..	..	..	..	..	..	..	..	..	..	..	+	+	..	+	..	..	..	..	..	Progressive financial inadequacy, coupled with indifference by girl and her parents as to her status, led to nonobservation of regimen as prescribed as long as diabetic emergencies were avoided
38x	+	..	..	..	..	..	..	..	..	..	..	..	..	..	+	+	+	..	..	+	..	..	..	Resources adequate, but neither patient nor her parents appreciated need for care which went beyond apparent immediate needs of her diabetic condition
11y	+	..	..	..	..	..	..	..	..	..	..	..	..	..	..	+	+	+	..	+	..	..	..	Boy's status resembled that of two preceding subjects; subsequent to completion of this study, he admitted that he never had taken cod liver oil while at home
81y	+	..	..	+	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Boy lived with a step-sister, and largely because of his indifference his regimen of diet was not maintained; become delinquent and later was committed to a state institution
62x	+	..	..	..	..	..	..	..	..	..	..	..	..	..	..	+	+	..	..	..	+	+	..	Girl's diabetes never was properly controlled at times when she reported for examination; it was inferred that her diet was not followed more faithfully than her diabetic management; she died later with diabetic complications
14y	+	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	+	+	..	+	..	..	+ Boy lost five sound teeth because of periodontoclasia, which was far advanced when he was first examined; lesions of enamel, presumably caries, developed on seven tooth surfaces
20y	+	+	..	..	+	..	..	..	+	+	+	..	+	+	+	..	..	..	..	..	..	+	..	Boy had complete alopecia from early childhood, had lived in a succession of foster homes; despite social handicaps, he maintained diabetic and dietary control fairly well

socioeconomic barriers to adequate care were present in some of the homes at the outset. Others developed because of problems imposed by the diabetes. In some homes social difficulties were alleviated purposefully when evidence was offered the parents that existing conditions were not favorable for the child's welfare. In other homes prolonged adherence to the regimen was followed by lax observance. In either instance, a period of observance was associated with freedom from advancing caries and a period of nonconformance by furtherance of caries. Some children subsisted on a regimen which met requirements in most but not all regards. This was true especially as it relates to the taking of cod liver oil. Omission of the oil did not precipitate a break in the level of diabetic management, and subjects who were less conscientious tended to discontinue its use unless periodically checked regarding it. Progression of caries led to the discovery of the omission of cod liver oil from the diets of several children; with its subsequent use, further progression was not observable. It was the impression of those directing the study that cod liver oil was one of the dietary factors involved but not the only one. Even in children who did not use cod liver oil but who followed the prescribed diet in the main in other regards, the rate of advance of caries was significantly reduced. From chart 1 it will be noted that some children went for long periods without new cavities; then abruptly several developed. Some such instances may be correlated with rather extensive abandonment of the prescribed regimen; others seemed to reflect the manifestation of a cumulative factor which had been operative for some time.

The commonest gross deviation from the prescribed dietary pattern was the omission of cod liver oil; the most pronounced deviation was the flagrant use of whatever foods were available or desired as long as they did not precipitate diabetic emergencies. The limitation of the group studied to children who had been under observation for at least three years eliminated certain of the worst offenders. The fact that the patients remained under recurrent observation for a prolonged period indicated some degree of cooperation, even though in several instances the whole initiative was carried by the medical and social agencies.

The 3 subjects in whom notable increase in the number of defects developed in the enamel without corresponding increase in manifest caries deserve special consideration. In the absence of evidence to the contrary, these defects must be considered as acquired lesions, probably representing enamel caries. Usually such dental lesions may be expected to progress steadily toward unmistakable caries involving the underlying dentin as well. In these subjects, as well as in the series as a whole, these enamel lesions remained essentially stationary in progression for periods of years even though not treated by fillings or by chemical application. Eventually some of the enamel defects progressed to true caries; most of them did not. The fact that so few enamel lesions developed in the group as a whole and the further fact that lesions present showed so slight a tendency to advance may be taken as evidence that the regimen which was effective in lessening dentinal caries was equally effective in protecting the enamel from attack.

Peridental lesions have been described as commonplace in children with diabetes mellitus.[13] In our series of patients, only 1 child had noteworthy evidence of periodontoclasia. This boy, subject 14 y, became diabetic when he was 2 years old. Up to the age of 7 years, neither his diet nor his diabetes was well controlled. When he was first seen in this clinic, at the age of 7 years, several of his teeth were very loose. Subsequently, five extractions of noncarious permanent teeth became neces-

13. Rutledge, C. E.: Clinical and Roentgenographic Aspects of Teeth and Jaws of Juvenile Diabetics, J. Am. Dent. A. **27**:1740 (Nov.) 1940.

sary because of loss of supporting structure. There is no evidence available to establish the cause of the alveolar resorption. This boy is one of those in whom several defects in the enamel developed after completion of eruption of the twenty-eight permanent teeth. Subsequent to the study herein reported, in several of the areas of enamel caries in his teeth moderate degrees of dentinal caries have developed. Data for this boy are presented more in detail in chart 1 and in table 3.

SUMMARY AND CONCLUSIONS

The records of prolonged observations of the teeth of 111 children with diabetes mellitus have been reviewed individually to establish the rate of dental decay and to compare it with the rate reported for normal children. The data are presented in order to establish the pronounced lowering of progress of caries in the group of children studied. Whereas the majority of subjects had little or no extension of caries for periods of years, a high rate of progression was noted intermittently or consistently among a small number who failed to observe the dietary regimen consistently in whole or in part. It is concluded that the incidence of caries during childhood can be lessened impressively through dietary means.

INGESTION OF FLUORIDE AND DENTAL CARIES

QUANTITATIVE RELATIONS BASED ON FOOD AND WATER REQUIREMENTS OF CHILDREN ONE TO TWELVE YEARS OLD

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With few exceptions the biochemistry of fluorine emphasizes its toxic features. The production of endemic dental fluorosis (mottled enamel) in human beings by fluorine in drinking water [1] is an outstanding example of the toxic effect of an excessive intake of the element. The recent discovery of the inhibitory effect of trace quantities of fluorine in drinking water on dental caries in children aged 12 to 14 years [2] and in young adults [3] marks the first indication that fluorine may have a beneficial role in animal physiology. This inhibitory effect of fluorine on dental caries is shown by data in table 1 and in the chart, taken from a recent report by Dean, Arnold and Elvove.[2b] The figures in table 2 are from a report by Deatherage [3] based on results of dental examinations of selectees of the current Selective Service law. The effect of fluorine present in drinking water is most striking, the total incidence of dental caries being reduced a third to one half by this water-borne element.

Prior to the discovery of the fluorine–dental caries association, any suspicion as to the physiologic importance of fluorine gained support principally from the observation that fluorine was present in trace quantities in many plant and animal tissues. Even this widespread occurrence of fluorine seemed accidental. In general, interest centered in the relation of fluorine to calcified tissues, i. e. the bones and teeth. Gautier and Clausmann [4] and Gautier [5] have speculated on the association of fluorine with the hardness and the resistance (*d'inaltérabilité chimique*) of body tissues which they found to contain the most notable quantities of fluorine. The improved performance of dental tissue (resistance to caries) due to the ingestion of fluorine may possibly agree with Gautier's hypothesis. Although the data are somewhat limited, the results of Armstrong and Brekhus [6] suggest that carious teeth may actually contain less fluorine than noncarious teeth.

While the observed fluorine–dental caries relation is suggestive of the effect of a trace element, it cannot be said that fluorine is an essential element of the diet in the accepted sense of the term. It has not been shown that the complete withdrawal of fluorine from otherwise adequate diets produces fatal or disabling symptoms. Dental caries cannot be classified as a fluorine deficiency disease until it has been demonstrated that inadequate amounts of fluorine in the diet invariably produce the disease. Thus far such observations have not been made. Attempts have been

1. Dean, H. T., in Gordon, S. M.: Dental Science and Dental Art, Philadelphia, Lea & Febiger, 1938.

2. (*a*) Dean, H. T.; Jay, P.; Arnold, F. A., and Elvove, E.: Pub. Health Rep. **56**:761, 1941. (*b*) Dean, H. T.; Arnold, F. A., and Elvove, E.: ibid. **57**:1155, 1942.

3. Deatherage, C. F.: Mottled Enamel from the Standpoint of the Public Health Dentist, in Publication 19, American Association for the Advancement of Science, 1942.

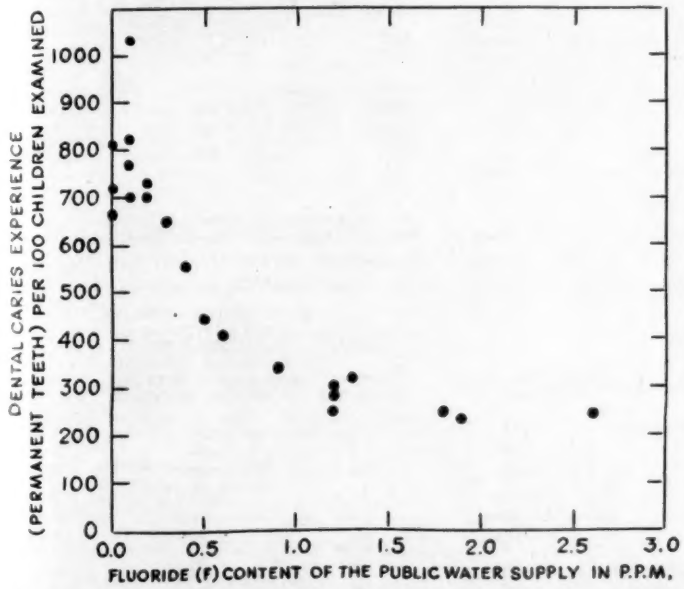
4. Gautier, A., and Clausmann, P.: Compt. rend. Acad. d. sc. **157**:94, 1913.

5. Gautier, A.: Compt. rend. Acad. d. sc. **158**:159, 1914.

6. Armstrong, W. D., and Brekhus, P. J.: J. Dent. Research **17**:393, 1938.

made to test the necessity of fluorine in the diet,[7] the white rat being used as the experimental subject. While dietary fluorine was reduced to an extremely low level in these studies, particularly in the experiment by Sharpless and McCollum,[7a] traces of fluorine still remained in these diets. The results of these experiments gave no evidence that the rat requires fluorine. In contrast to the human subject, however, the rat has not proved to be notably susceptible to spontaneous dental caries.

The hygienic value of fluorine as a preventive of caries suggests the inclusion of fluorine in the diet in certain optimum amounts. The dental tissues are extremely sensitive to fluorine during the formative period, i. e., during the first seven or eight years of life (with exclusion of the third molar teeth, which are not completely developed until the twelfth or fourteenth year). The addition of fluorine to children's diets during the first seven or eight years of life offers great promise of reducing the prevalence of dental caries. At the present time the quantity of fluorine



Relation between the incidence of dental caries in permanent teeth observed in 7,257 selected 12 to 14 year old white school children of twenty-one cities of four states and the fluoride content of the public water supply (from Dean, Arnold and Elvove [2b]).

in the diet associated with caries-inhibitory effects is defined in terms of fluorine present in drinking water. As shown in table 1, such quantities are of the order of 0.5 to 1.4 parts per million or more. In consideration of the significance of the fluorine–dental caries relation and the thereby enhanced nutritional importance of fluorine, it is desirable to have some idea of the approximate quantities being ingested daily in food and certain drinking waters. The figures in table 3 are presented, therefore, to show the approximate quantities of fluorine ingested daily through the use of drinking water containing 1 part per million and in the consumption of food containing trace amounts. One part per million was selected as the concentration of fluorine in drinking water because according to both the epidemiologic evidence [2a] and the standards for drinking water of the Public Health

7. (*a*) Sharpless, G. R., and McCollum, E. V.: J. Nutrition **6**:163, 1933. (*b*) Evans, R. J., and Phillips, P. H.: ibid. **18**:353, 1939.

Service [8] this is a permissible level. While final judgment regarding the possibility of other physiologic effects resulting from this quantity of fluorine (1 part per million) in drinking water is not justified, the evidence available at this time does not suggest that harm will result when this much fluorine is present in children's diets from perhaps the age of 1 year through the seventh or eighth year or even to an older age.

Drinking of water is a variable factor, especially among children, whose drinking habits are greatly influenced by muscular activity as well as by atmospheric temperature and humidity. It is likewise true of children's diets especially that the requirement of water is met largely by preformed water in the food or by liquid food,

TABLE 1.—*Relation of Fluorine Concentration of Public Water Supplies and Dental Caries (Data from Dean, Arnold and Elvove [2b])*

Number of Children Examined	Age, Years	Total Incidence of Dental Caries (Missing Teeth, Untreated Teeth and Filled Teeth per 100 Children)	Fluorine in Public Water Supply, Parts per Million
3,867	12-14	745	<0.5
1,140	12-14	425	0.5 to 0.9
1,403	12-14	300	1.0 to 1.4
847	12-14	250	>1.4

TABLE 2.—*Dental Caries Experience of Draft Selectees Living in Endemic Fluorine Areas Compared with Selectees Living in Nonendemic Areas (Data from Deatherage [3])*

	Age, Years	Number Examined	Total Incidence of Caries (Teeth with Untreated Caries, Filled Teeth, Extraction Indicated and Missing Teeth per 100 Selectees Examined)	Area *
Entire life spent in respective areas	21-24	130	510	Endemic
	21-24	112	1,011	Nonendemic
	25-28	34	609	Endemic
	25-28	52	1,029	Nonendemic
	All ages	164	530	Endemic
	All ages	164	1,016	Nonendemic
First eight years, but not entire life spent in respective areas	21-28	77	581	Endemic
	21-28	82	1,077	Nonendemic

* Endemic areas are those where fluorine in the drinking water causes mottled enamel. Fluorine, although causing the teeth to be mottled if present in quantities above 1 part per million in drinking water, also inhibits dental caries in these larger amounts.

particularly milk. The water deficit made up by drinking water may be a relatively small fraction of the total daily amount of water ingested. For the estimates of ingestion of water as drinking water per se, as shown in table 3, the method of estimating the daily water requirement of the average child and adult proposed by Adolph [9] was adopted. Adolph estimated the daily water requirement as equal to 1 cc. per calory of energy in the daily diet. In consideration of the numerous factors influencing water-drinking habits, two estimates of the amount of water drunk have been made: (*a*) Drinking water was estimated to equal 25 per cent

8. Public Health Service Drinking Water Standards, Report of Advisory Committee on Official Water Standards, Pub. Health Rep. **58**:69, 1943. Public Health Service Drinking Water Standards, J. Am. Water Works A. **35**:93, 1943.

9. Adolph, E. F.: Physiol. Rev. **13**:336, 1933.

of the daily requirement and (*b*) to equal 33 per cent of this requirement. These approximations apply to children's drinking habits extending over an entire year in a temperate climate. No doubt considerable fluctuation would occur throughout the year and average quantities drunk would vary somewhat with the climate.

The figures for water consumption in table 3 may be compared with other estimates and actual measurements of water drinking. Macy [10] found that the total

TABLE 3.—*Estimated Daily Intake of Fluorine from Drinking Water Containing 1 Part per Million of Fluorine and from Food Containing 0.1 to 1 Part per Million of Fluorine in the Dry Substance*

Age (years)	1 to 3	4 to 6	7 to 9	10 to 12
Energy allowance (calories)	1,200	1,600	2,000	2,500
Water requirement (cc.)	1,200	1,600	2,000	2,500
Drinking water consumption				
(1) When water drunk is equal to 25 per cent of the total daily water requirement and (*a*) 10 per cent and (*b*) 20 per cent of the total water content of the food is of drinking water origin, the total daily conumption of drinking water would equal:				
(*a*)	390 cc.	520 cc.	650 cc.	812 cc.
(*b*)	480 cc.	640 cc.	800 cc.	1,000 cc.
(2) When water drunk is equal to 33 per cent of the total daily water requirement and (*c*) 10 per cent and (*d*) 20 per cent of the total water content of the food is of drinking water origin, the total daily consumption of drinking water would equal:				
(*c*)	480 cc.	640 cc.	800 cc.	1,000 cc.
(*d*)	560 cc.	746 cc.	933 cc.	1,166 cc.
Total daily fluorine ingested from drinking water containing 1 part per million of fluorine under the preceding conditions of water ingestion would equal:				
In water intake (*a*)	0.390 mg.	0.520 mg.	0.650 mg.	0.810 mg.
In water intake (*b*) and (*c*)	0.480 mg.	0.640 mg.	0.800 mg.	1.000 mg.
In water intake (*d*)	0.560 mg.	0.745 mg.	0.930 mg.	1.165 mg.
Total dry substance in daily food allowance when 1 Gm. of dry substance of the food furnished 4.5 calories of energy				
Total daily intake of dry substance	265 Gm.	355 Gm.	445 Gm.	555 Gm.
Fluorine ingested daily in food in which the dry substance of the food contained the following concentrations of fluorine:				
(*a*) 0.10 part per million	0.027 mg.	0.036 mg.	0.045 mg.	0.056 mg.
(*b*) 0.20 part per million	0.053 mg.	0.071 mg.	0.089 mg.	0.111 mg.
(*c*) 0.50 part per million	0.133 mg.	0.178 mg.	0.223 mg.	0.278 mg.
(*d*) 1.00 part per million	0.265 mg.	0.360 mg.	0.450 mg.	0.560 mg.
Estimated total daily fluorine ingested in food and drinking water:				
Food (*a*) plus water (*a*)	0.417 mg.	0.556 mg.	0.659 mg.	0.866 mg.
Food (*b*) plus water (*a*)	0.443 mg.	0.591 mg.	0.739 mg.	0.921 mg.
Food (*c*) plus water (*a*)	0.523 mg.	0.698 mg.	0.872 mg.	1.088 mg.
Food (*d*) plus water (*a*)	0.653 mg.	0.880 mg.	1.100 mg.	1.370 mg.
Food (*a*) plus water (*b*) or (*c*)	0.507 mg.	0.676 mg.	0.845 mg.	1.056 mg.
Food (*b*) plus water (*b*) or (*c*)	0.533 mg.	0.711 mg.	0.889 mg.	1.111 mg.
Food (*c*) plus water (*b*) or (*c*)	0.613 mg.	0.818 mg.	1.023 mg.	1.278 mg.
Food (*d*) plus water (*b*) or (*c*)	0.745 mg.	1.000 mg.	1.250 mg.	1.560 mg.
Food (*a*) plus water (*d*)	0.587 mg.	0.781 mg.	0.975 mg.	1.221 mg.
Food (*b*) plus water (*d*)	0.613 mg.	0.816 mg.	1.019 mg.	1.276 mg.
Food (*c*) plus water (*d*)	0.693 mg.	0.923 mg.	1.153 mg.	1,443 mg.
Food (*d*) plus water (*d*)	0.825 mg.	1.105 mg.	1.380 mg.	1.725 mg.

amount of water consumed daily by children 8 to 12 years of age ranged from 1,658 to 1,745 cc.; 449 to 568 cc. of these amounts, i. e. about 25 to 30 per cent, was ingested as drinking water. Richter and Brailey [11] regarded 2,400 cc. as a good average for water intake daily by an average man weighing 65 Kg. Another estimate of the average water requirement of children aged 1 to 18 years is 1,100

10. Macy, I. G.: Nutrition and Chemical Growth: Evaluation, Springfield, Ill., Charles C Thomas, Publisher, 1942, vol. 6.

11. Richter, C. P., and Brailey, M. E.: Proc. Nat. Acad. Sc. **15**:570, 1929.

to 2,700 cc. daily.[12] Magee [13] studied the fluid intake of persons aged 8 to 80 years. Total water consumed, i. e. raw water, including water used in cooking, averaged 1,324 cc. for males and 1,551 cc. for females daily. Additional water in milk and other foods accounted for a total daily water intake of 2,081 cc. for males and 2,195 cc. for females. Rowntree [14] estimated the average diet (food) to contain 1,000 cc. of water daily, made up of water naturally in food, water from oxidation of food and water added during cooking. The remainder of the total daily water requirement would be supplied by water drunk per se, and by other beverages. These later quantities totaled about 1,200 to 1,600 cc. daily. In a previous publication I estimated the average daily consumption of drinking water by the average

TABLE 4.—*Fluorine Content of Foods as Reported in the Literature* *

Food	Fluorine, Parts per Million	Food	Fluorine, Parts per Million
Fluorine Reported in Food as Consumed			
Milk	0.07-0.22	Pork chop	1.00
Egg white	0.00-0.60	Frankfurters	1.70
Egg yolk	0.40-2.00	Round steak	1.30
Butter	1.50	Oysters	1.50
Cheese	1.60	Herring (smoked)	3.50
Beef	<0.20	Canned shrimp	4.40
Liver	1.50-1.60	Canned sardines	7.30-12.50
Veal	0.20	Canned salmon	8.50- 9.00
Mutton	<0.20	Fresh fish	1.60- 7.00
Chicken	1.40	Canned mackerel	26.89†
Pork	<0.20		
Fluorine Reported in Dry Substance of Food			
Rice	<1.00	Honey	1.00
Corn	<1.00	Cocoa	0.50-2.00
Corn (canned)	<0.20	Milk chocolate	0.50-2.00
Oats	1.30	Chocolate (plain)	0.50
Crushed oats	<0.20	Tea (various brands)	30.00-60.00
Dried beans	0.20	Cabbage	0.31- 0.50
Whole buckwheat	1.70	Lettuce	0.60- 0.80
Wheat bran	<1.00	Spinach	1.00
Whole wheat flour	1.30	Tomatoes	0.60-0.90
Biscuit flour	0.00	Turnips	<0.20
Flour	1.10-1.20	Carrots	<0.20
White bread	1.00	Potato (white)	<0.20
Ginger biscuits	2.00	Potato (sweet)	<0.20
Rye bread	5.30	Apples	0.80
Gelatin	0.00	Pineapple (canned)	0.00
Dextrose	0.50	Orange	0.22

* For the source of these analytic data see McClure.[15]
† Lee and Nielson.[21]

adult to equal 1,200 to 1,500 cc.[15] For an excellent discussion of water metabolism the article by Adolph [9] should be consulted.

Water added to food during cooking processes is probably more unpredictable than any of the various factors involved in estimating water ingestion. In order to account for the addition of a quantity of fluorine to food during cooking, the calculations in table 3 include estimates of (*a*) 10 per cent and (*b*) 20 per cent of the total food-borne water as consisting of water of drinking water origin.

12. Growth and Development of the Child: III. Nutrition, White House Conference on Child Health and Protection, New York, Century Company, 1932, p. 316.

13. Magee, H. E.: J. Hyg. **37**:30, 1937.

14. Rowntree, L. G.: Physiol. Rev. **2**:116, 1922.

15. McClure, F. J.: Fluorides in Food and Drinking Water, National Institute of Health Bulletin 172, United States Treasury Department, Public Health Service, 1939.

The amount of fluorine ingested in food seems also to be surrounded with considerable uncertainty. Analytic methods for determination of fluorine have not progressed to the point where trace quantities, such as occur in most foods, can be determined with entire satisfaction. A list of foods and food constituents and their fluorine content as reported in the literature, is shown in table 4. Most foods appear to contain somewhat less than 1 part of fluorine per million parts of dry substance. Although fish foods and teas may contain on the average as much as 8 to 12 and 30 to 60 parts per million of fluorine respectively, these foods do not usually occur in appreciable quantities in children's diets. Because of obvious uncertainties surrounding the quantity and quality of various foods in children's diets, four levels of fluorine in foods have been selected as falling within the range apt to be present in the mixed dry substance of the average diet.

The calory allotments shown in table 3 are taken from recent standards set by the Committee on Food and Nutrition of the National Research Council.[16] The total dry substance of the diet has been estimated on the assumption that 1 Gm. of dry substance comprising the average mixed diet will have an average energy value of 4.5 calories. The total dry substance was estimated, therefore, by dividing the calory allotment by this figure. The fluorine content of the diet was based on this estimate of dry substance.

In observations on young rats, Lawrenz, Mitchell and Ruth [17] and Lawrenz and Mitchell [18] found that about 20 per cent more of water-borne fluorine was assimilated than of fluorine ingested in food. This impairment of assimilation of fluorine due to the presence of food in the alimentary tract was observed when rigid control was exercised over the animals' habits of eating and drinking. This observed difference in assimilation of fluorine would need to be taken into consideration if similar conditions surrounded ingestion of fluorine by human subjects, as in case an allotment of fluorine in the diet was ingested entirely in the food or the fluorine-containing water was ingested on an empty stomach. Results obtained by me [15] relative to water-borne vs. food-borne fluorine, when no control was exercised over eating and drinking habits, gave no indications of a difference in total assimilation of fluorine in young rats. In this test the presence of food in the alimentary tract during any drinking period obviously obscured the effect of water-borne fluorine per se. These results also would be applicable only if the drinking habits of the rat and of man were similar. Considering the uncertainties surrounding individual drinking habits, a difference in the hygienic effect of fluorine ingested in food as compared with fluorine ingested in drinking water has not been applied to the figures given in table 3. In regard to the effects of fluoride in food alone the following facts may be noted: (*a*) Fluorine in water and fluorine in food both have inhibitory effects on experimental caries in rats [19]; (*b*) endemic dental fluorosis (mottled enamel) appears to result from food-borne and water-borne fluorine [20]; (*c*) Lee and Nielson found that fluorine contained in fish was assimilated by young

16. Recommended Dietary Allowances, Committee on Food and Nutrition, National Research Council, May 1941.

17. Lawrenz, M.; Mitchell, H. H., and Ruth, W. A.: J. Nutrition **18**:127, 1939.

18. Lawrenz, M., and Mitchell, H. H.: J. Nutrition **22**:621, 1941.

19. Miller, B. F.: Proc. Soc. Exper. Biol. & Med. **39**:389, 1938. Finn, S. B., and Hodge, H. C.: J. Dent. Research **18**:252, 1939. Cheyne, V. D.: Proc. Soc. Exper. Biol. & Med. **43**:58, 1940. Cox, G. J.; Matuschak, M. C.; Dixon, S. F.; Dodds, M. L., and Walker, W. E.: J. Dent. Research **18**:481, 1939. McClure, F. J.: J. Nutrition **22**:391, 1941.

20. Sognnaes, R. F.: J. Dent. Research **20**:303, 1941.

rats,[21] and (*d*) fluorine in tea is assimilated and produces characteristic effects experimentally.[22]

The estimates of fluorine intake shown in table 3 may be compared with the actual fluorine content of an average diet consumed by a man, as determined by Machle, Scott and Largent.[23] The actual fluorine intake based on a nine month study was approximately 0.45 mg. daily. The drinking water contained no fluorine, all the dietary fluorine being ingested in food and beverages. It was noted that almost twice as much fluorine was contributed by fluids (tea, coffee, milk, beverages and beer) as was present in the solid food. As would be expected, the consumption of iced tea during the summer seemed to account for a notable elevation in intake of fluorine.

In table 5 are summary estimates of fluorine intake such as appear in table 3. The quantity of fluorine ingested by children from drinking water containing 1 part per million of fluorine according to these estimates will equal approximately 0.5 to 1 mg. of fluorine daily. This quantity of water-borne fluorine plus fluorine contained in foods may bring the total amount of fluorine contained in the average daily diet up to 1 to 1.50 mg. The ratio of these approximate levels of intake to

TABLE 5.—*Summary of Estimated Daily Intake of Fluorine from Food and From Drinking Water (Drinking Water Containing 1 Part per Million of Fluorine and Dry Substance of Food Containing 0.1 to 1 Part per Million of Fluorine)*

Age, Years	Body * Weight, Kg.	Daily Fluorine Intake			
		From Drinking Water, Mg.	From Food, Mg.	Total Daily from Food and Drinking Water, Mg.	Total Daily, Mg./Kg. of Body Weight
1 to 3	8 to 16	0.390-0.560	0.027-0.265	0.417-0.825	0.026-0.103
4 to 6	13 to 24	0.520-0.745	0.036-0.360	0.556-1.105	0.023-0.085
7 to 9	16 to 35	0.650-0.930	0.045-0.450	0.695-1.380	0.020-0.088
10 to 12	25 to 54	0.810-1.165	0.056-0.560	0.866-1.725	0.016-0.069

* Figures for weight for ages 1 to 6 years were taken from tables arranged by Woodbury (Woodbury, R. M.: Statures and Weights of Children Under Six Years of Age, Publication 87, U. S. Department of Labor, Children's Bureau, 1921); figures for 6 to 12 years were taken from the Baldwin-Wood weight-height-age tables for boys and girls of school age, published by the American Child Health Association.

body weight would probably rarely exceed 0.1 mg. per kilogram of body weight (table 5). As a general rule this average would equal about 0.05 mg. daily per kilogram of weight for children of these age groups.

SUMMARY

An estimated quantity of water-borne fluorine equal to approximately 0.5 to 1 mg. of fluorine daily present in the average diet from the first to the eighth year of life appears to be instrumental in reducing dental caries to a great degree. There has been no evidence presented heretofore to compare with this mass reducduction of caries accompanying a modification of a dietary factor.

While conclusions may be modified by further experimental and clinical studies, at this time the evidence does not indicate that a health hazard surrounds this small quantity of additional fluorine ingested during the comparatively few years of

21. Lee, C. F., and Nielson, H. W.: Study of the Metabolism of Naturally Occurring Fluorine in Canned Salmon and Mackerel, Investigational Report 44, United States Department of Commerce, Bureau of Standards, 1939.

22. Reid, E.: Chinese J. Physiol. **10**:259, 1936. Lawrenz, Mitchell and Ruth.[17]

23. Machle, W.; Scott, E. W., and Largent, E. J.: J. Indust. Hyg. & Toxicol. **24**:199, 1942.

formative tooth life. The importance of the preventive effects of fluorine on dental caries suggests that serious thought be given to the use of this optimum quantity of supplemental fluorine in children's diets for the partial control of dental caries.

In certain communities the drinking water may contain fluorine naturally in a quantity equal to 1 part of fluorine per million. In these places a supplement of dietary fluorine obviously would be unnecessary and undesirable. There is under consideration also the advisability of a direct fluorination of drinking water [24] so as to provide an optimum quantity of fluorine for improved dental health. Under this condition, likewise, the previous recommendation for additional fluorine in the diet would not apply. Therefore, only in communities in which the water supplies either are fluorine free or contain suboptimal amounts of fluorine need serious consideration be given to the possible use of a supplement of fluorine in children's diets. Calculations of the quantity of supplemental fluorine required must take into account fluorine present naturally in the local water supply.

National Institute of Health.

24. Arnold, F. A., Jr.: J. Am. Dent. A. **40**:499, 1943.

PANCREATIC FUNCTION AND DISEASE IN EARLY LIFE

II. EFFECT OF SECRETIN ON PANCREATIC FUNCTION OF INFANTS AND CHILDREN

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The use of secretin as a test substance for the study of pancreatic function has increased extensively in recent years but has been limited, as far as can be determined, to normal adults and to adult patients.[1] The studies reported here were carried out to supply data concerning the effect of secretin on the pancreatic function of infants and children and to ascertain its usefulness as a diagnostic aid in studies of pancreatic disease in early life.

The discovery by Bayliss and Starling in 1902 of the hormone secretin was followed by numerous unsuccessful attempts to make clinical use of this observation.[1a] The recent isolation of secretin from the intestinal mucosa as a crystalline salt, by Hammarsten, and the preparation by Agren of a substance suitable for clinical work have permitted a number of investigations of the action of secretin within the last few years.[1a] As observed on adults, the effect of secretin administered intravenously is noticeable usually within a minute. The normal bile-stained duodenal content becomes paler, and often a clear, almost colorless secretion may be obtained. After a short time the yellowish color of the duodenal content reappears. Its volume increases markedly and reaches its peak within the first ten minutes after the injection of secretin. The p_H usually reaches a value of 8 or more, and the content of bicarbonate is increased. The concentration of enzymes in the pancreatic juice declines, reaching its low point in the second ten minute period. The total value for each enzyme per unit of time is increased, but the increase is limited almost entirely to the first ten minute period. The increase in total values appears to be produced by a washing out of preformed enzymes and not by any effect of secretin on new formation of pancreatic enzymes. Pratt has observed an abundant flow of pancreatic juice, which amounts usually to 150 cc. in one hour after the injection of secretin, and in one instance he was able to collect 100 cc. in ten minutes.[1b] Ivy and his co-workers stated that the activity of the enzymes may vary in a random fashion following the intravenous administration of secretin.[2b]

These studies were supported by a grant from the Ann Proctor Rice Fund, of Harvard Medical School.

From the Children's Hospital and the Infants' Hospital, Boston, and the Department of Pathology, Harvard Medical School.

1. (*a*) Lagerloef, H. O.: Pancreatic Function and Pancreatic Disease, New York, The Macmillan Company, 1942. (*b*) Pratt, J. H.: Pancreatic Disease, J. A. M. A. **120**:175 (Sept. 19) 1942. (*c*) Diamond, J. S.; Siegel, S. A., and Myerson, S.: The Secretin Test as an Aid in the Differential Diagnosis of Steatorrheas with a Report of Fourteen Cases, Rev. Gastroenterol. **7**:429, 1940.

2. (*a*) Lagerloef.[1a] Pratt.[1b] Diamond, Siegel and Myerson.[1c] (*b*) Voegtlin, W. L.: Greengard, H., and Ivy, A. C.: The Response of the Canine and Human Pancreas to Secretin,

(Footnote continued on next page)

Diamond and his co-workers found that the concentration curve for the three main pancreatic enzymes is uniform, with the least amount of change in the activity of lipase.[1c] That the secretin test may be of real diagnostic value has been shown by recent investigations. Pratt, for example, was able to study the function of the pancreas before and after the use of secretin in 5 proved cases of cancer of the pancreas.[1b] Without the secretin test no evidence of pancreatic insufficiency would have been discovered in 4 of the 5 patients. On 2 occasions Pratt observed transitory hypochylia pancreatica with reduction in volume, alkalinity and enzymatic activity to levels as low as those in cancer of the pancreas. Since no similar instances have been observed by others who have employed the secretin test, Pratt believed it proper to assume the presence of organic disease of the pancreas if low values are found after the injection of secretin.

PRESENT STUDIES

The duodenal content was obtained and analyzed before and after the intravenous administration of secretin to normal infants and children and to patients suffering from idiopathic celiac disease, pancreatic fibrosis, chronic nutritional disturbance and in one instance selective trypsin deficiency. There were twenty-six determinations made on 21 patients, who varied in age from 6 weeks to 11 years. The diagnosis of pancreatic fibrosis was made in 7 cases in which pancreatic achylia or hypochylia was proved by the actual analysis of tryptic, lipolytic and amylolytic activity.[3] As has been stated, pancreatic achylia or hypochylia has been found always in association with the obstructive lesion of pancreatic fibrosis. The 2 patients with idiopathic celiac disease had all of the usual clinical and laboratory findings necessary for that diagnosis. Failure to gain in weight was the most important complaint of the patients with chronic nutritional disturbance. When first seen, these patients gave a history of gastrointestinal disturbances, such as diarrhea, intolerance to certain foods, anorexia and occasionally vomiting. Patients presenting symptoms of the celiac syndrome secondary to chronic infection are included in this group. Other data concerning the activity of the pancreatic enzymes of the patients referred to here have been described in a previous communication.[3a]

The duodenal content was removed, and the activity of the pancreatic enzymes analyzed according to technic and methods described elsewhere.[3b] The patient was kept in a fasting state for at least six hours before the study was begun. The fluid was collected in ten to twenty minute periods for approximately one hour before the intravenous injection of secretin. Specimens were collected from time to time during the succeeding hour.

The secretin (Astra) employed was a powdered preparation known commercially as "pancreotest" and originally obtained from Södertälje, Sweden. Each ampule contained 40 mg., or 80 clinical units. The amount given was calculated on the basis of weight; 1 mg. per kilogram of body weight was the standard dose. This preparation of secretin was found by Ivy and his co-workers to possess half the potency of the standard secretin prepared by them and used on human subjects. The material was dissolved fresh in approximately 2 to 5 cc. of isotonic solution of sodium chloride, boiled for three minutes and given intravenously. No systemic reaction or untoward effect was noted. In 1 instance repeated administration at intervals of nine, ten and thirteen months and in another instance administration at intervals of nine months after the initial injection likewise caused no reaction. Pratt injected secretin into nearly 100 adults without untoward results and found that a second injection in the same subject produced no unpleasant symptoms.[1b]

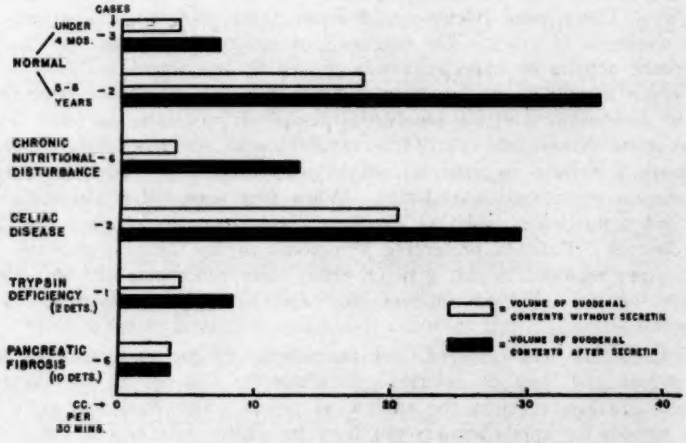
Am. J. Physiol. **110**:198, 1934. (*c*) Greengard, H., and Stein, I. F.: Assay of Secretin, Proc. Soc. Exper. Biol. & Med. **46**:149, 1941. (*d*) Comfort, M. W.: Tests of Pancreatic Function, J. A. M. A. **115**:2044 (Dec. 14) 1940. (*e*) La Barre, J.: La sécrétine, Paris, Masson & Cie, 1936.

3. (*a*) Farber, S.; Maddock, C. L., and Shwachman, H.: Pancreatic Enzyme Activity and the Celiac Syndrome, J. Clin. Investigation, November 1943, to be published. (*b*) Shwachman, H.; Farber, S., and Maddock, C. L.: Prancreatic Function and Disease in Early Life: III. Methods of Analyzing Pancreatic Enzyme Activity, Am. J. Dis. Child., this issue, p. 418.

The volume of fluid, the time of collection, the p_H, the color and the viscosity were recorded. The concentrations of trypsin, amylase and lipase in many fractional specimens were determined. The concentration of bicarbonate was determined by direct titration in some specimens.

EFFECT OF SECRETIN ON VOLUME AND APPEARANCE OF DUODENAL FLUID

The increased flow of duodenal juice that followed the injection of secretin occurred in three to five minutes in the majority of patients. Often the pancreatic flow was so copious that the bile coloring of the duodenal fluid was diluted so that the fluid was colorless by the end of twenty minutes, at which time the rate of flow diminished. The accompanying chart illustrates the effect of secretin on the volume of pancreatic drainage. The values at thirty minutes are given, since the most significant change in volume after stimulation with secretin is attained by this time. The thirty minute postinjection value is compared with the average volume of drainage in the same length of time prior to the injection, although often the total collection of fluid lasted more than two hours.



Effect of "pancreotest" on volume of duodenal contents.

The most striking feature of the chart is the small volume obtained in patients with pancreatic fibrosis and the apparent failure of secretin to stimulate pancreatic flow in these patients. Because the duodenal content of these patients is exceedingly thick and viscid, it is difficult for one to pipet or pour from one tube to another. Constant suction applied to the end of the duodenal tube is often necessary to obtain the sample, whereas with the other patients studied this was not necessary. For this reason the data on volume may not be so accurate as those for the other groups studied. In the cases of less advanced pancreatic fibrosis the postinjection fluid did become less viscous and the flow somewhat more abundant after stimulation with secretin. Further observations may bear out this suggestion that the response to secretin may be an indication of the degree of pancreatic involvement.

The 6 patients with chronic nutritional disturbance and the 2 patients with idiopathic celiac disease showed an excellent response to secretin. A large volume of pancreatic drainage per unit of time without stimulation with secretin appears to be characteristic of patients with idiopathic celiac disease. The response to this substance in the child with selective trypsin deficiency resembled that of normal persons or of patients with chronic nutritional disturbance rather than that of patients with pancreatic fibrosis.

THE EFFECT OF SECRETIN ON PANCREATIC ENZYME ACTIVITY IN THE DUODENAL CONTENT

It was impossible to obtain data concerning the volume of the duodenal content and the activity of the enzymes in five or ten minute periods for a number of subjects sufficient to permit adequate comparison. It was decided, therefore, to present the data concerning activity of the enzymes on the basis of total activity for one hour before and for one hour after the injection of secretin. It is, of course, clear that complete removal of the duodenal drainage is not possible.

Effect on Tryptic Activity.—The normal infants and children and the patients with chronic nutritional disturbance reacted in about the same degree, with an appreciable increase in tryptic activity, after the injection of secretin. There was a slight increase in tryptic activity in the patients with pancreatic fibrosis, but the increase of actual units for one hour after the injection of secretin was so small as to be considered negligible. No explanation can be offered for the slight but definite decrease in tryptic activity in the patients with idiopathic celiac disease. Secretin had no effect on the zero value in the patient with selective trypsin deficiency.

Total Activity of Enzymes in Units for One Hour Before and for One Hour After Stimulation with Secretin

	Cases	Trypsin B	Trypsin A	Lipase B	Lipase A	Amylase B	Amylase A
Normal infants and children	5	4,325	6,720 (+55%)	1,573	2,682 (+70%)	3,293	5,780 (+75%)
Patients with pancreatic fibrosis	7	21.6	26.4 (+22%)	13.7	9.4 (−31%)	216.3	137.5 (−36%)
Patients with chronic nutritional disturbance	6	2,769	4,253 (+54%)	482	1,191 (+146%)	1,090	3,534 (+224%)
Patients with celiac disease	2	11,715	7,480 (−36%)	1,507	3,070 (+104%)	6,560	5,000 (−24%)
Patients with trypsin deficiency (2 determinations)	1	0	0	397	1,147 (+189%)	1,610	3,200 (+99%)

Effect on Lipolytic Activity.—A definite increase in lipolytic activity was observed in the normal infants and children. The greatest increase occurred in the patient with selective trypsin deficiency. Those with chronic nutritional disturbance and with idiopathic celiac disease followed in that order, and in both instances the increase was greater than in normal persons. There was a small but definite decrease in lipolytic activity after injection of secretin in the patients with pancreatic fibrosis.

Effect on Amylolytic Activity.—Secretin produced a moderate increase in amylolytic activity in the normal infants and children. There was greater increase in the patient with selective trypsin deficiency and a much greater increase in patients with chronic nutritional disturbance. Small but definite decreases in amylolytic activity were observed in the patients with celiac disease and in those with pancreatic fibrosis.

EFFECT OF SECRETIN ON p_H OF THE DUODENAL CONTENT

The p_H of the duodenal content before stimulation varied from 6.8 to 8.0. After stimulation of the pancreas with secretin the p_H was increased by approximately 0.5 in all subjects studied except in the patients with pancreatic fibrosis. The rise occurred in the first ten to twenty minutes after the injection and persisted in many instances for as long as forty minutes after the injection.

COMMENT

These preliminary observations support findings in previous tests made on adults concerning the value of secretin as an aid in the study of pancreatic function.[2] The number of observations made before and after the use of secretin is too small to permit final conclusions concerning the value of this substance in the study of pancreatic function in infants and children. In our limited experience no data concerning pancreatic function were obtained by stimulation with secretin which were not available from a study of the duodenal content before stimulation. Of interest was the demonstration that in patients with pancreatic achylia caused by pancreatic fibrosis no change in the duodenal drainage could be observed after one mechanical flushing of the pancreatic ducts and the acinar cells had been attempted by stimulation with secretin. For the differentiation of idiopathic celiac disease from pancreatic fibrosis, collection of the duodenal content without stimulation with secretin appears adequate. In studies of activity of pancreatic enzymes made of 22 patients with pancreatic fibrosis, controlled in 7 of them by stimulation with secretin, no misleading results were encountered. Attention should be directed, however, to the value of the secretin test in studies of the pancreatic function of adults, as reported by all who have used it. This is particularly true when the presence of carcinoma of the pancreas is suspected, as Pratt has pointed out.[1b]

Interest in the function of the pancreas of infants and children has been limited to a small number of conditions, the most important of which is pancreatic fibrosis. It is quite possible, therefore, that studies of activity of pancreatic enzymes in a large series of infants and children may disclose abnormalities now unsuspected. If stimulation with secretin should be used in all studies of pancreatic function, as is indicated from the reported studies on adults, it appears proper to inquire whether additional methods might not yield even more information. Comfort and Osterberg [4] recently have advocated investigation of the vagal mechanism as well as of the humoral (secretin) for the control of pancreatic function. These workers used mecholyl chloride (acetylbetamethylcholine chloride) for that purpose. Stimulation with secretin demonstrates that the normal pancreas is capable of producing a high volume of alkaline juice; stimulation with mecholyl chloride, that the normal pancreas is able to produce a juice rich in enzymes. It has been suggested that future studies of pancreatic function will not be regarded as complete unless the levels of the activity of the pancreatic enzymes in the duodenal content under the usual conditions of study are compared with those obtained after stimulation of the pancreas by secretin and by mecholyl chloride.

SUMMARY AND CONCLUSIONS

A report is given concerning the effect of stimulation with secretin of the pancreas of infants and children, of whom some were normal and others patients with celiac disease, chronic nutritional disturbance, pancreatic fibrosis and selective trypsin deficiency. Twenty-six determinations were made on the duodenal content of 21 infants and children before and after the injection of secretin. It was found that:

1. Secretin may be injected intravenously into infants and children without ill effects and may be given on more than one occasion without danger.

4. Comfort, M. W., and Osterberg, A. E.: Pancreatic Secretion in Man After Stimulation with Secretin and Acetylbetamethylcholine Chloride, Arch. Int. Med. **66**:688 (Sept.) 1940.

2. In normal infants and children and in patients with celiac disease and in those with chronic nutritional disturbance the injection of secretin was followed by an increase in volume and p_H of the duodenal content.

3. No important change in either volume or tryptic activity was produced by secretin in 7 patients with pancreatic fibrosis.

4. No change in tryptic activity was demonstrable in a boy with trypsin deficiency, although a decided increase in volume and in lipolytic and amylolytic activity was produced.

5. An increase in lipolytic activity was produced by stimulation with secretin in all subjects studied except in patients with pancreatic fibrosis, in whom a slight decrease was observed.

6. An increase in amylolytic activity was found in all subjects studied except in patients with pancreatic fibrosis and in those with celiac disease, in whom a slight decrease was observed.

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EFFECTS OF DISEASE ON NUTRITION

I. ABSORPTION, STORAGE AND UTILIZATION OF VITAMIN A IN THE PRESENCE OF DISEASE

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It is well known that in certain diseases malnutrition or wasting occurs despite the fact that the process itself does not involve primarily the gastrointestinal tract. A good example of such a disease is pulmonary tuberculosis, which received the name of consumption or phthisis. Jacobi [1] in 1889, discussing the symptomatology of tuberculosis in childhood, noted: "The children are thin and puny, or emaciate visibly, in spite of good and sufficient nourishment and fair digestion in the absence of fever." Recently in a study of malnutrition in infants conducted by one of the authors,[2] it became strikingly clear that disease in the form of chronic infection was the most important etiologic factor as regards failure of infants to gain weight. Of 1,000 infants admitted to a hospital with the chief complaint of failure to gain, only 10 per cent could be considered to have been badly fed. The failure of the remaining babies to gain weight seemed largely attributable to intrinsic factors, especially to disease in the infant. The current hospital methods of infant feeding were little more effective in overcoming the malnutrition than were the efforts of the family physician. The disease processes were often so obscure that in many instances the history did not indicate their presence, and it was only through careful and thorough physical examination supplemented by laboratory tests and roentgen evidence that detection occurred. The most frequently encountered causes of failure to gain were the presence of chronic pulmonary disease and chronic infection of the upper respiratory tract with postnasal discharge. Other common causes were infection of the urinary tract; congenital malformations, especially cardiovascular, gastrointestinal and renal, and gastrointestinal disease, including such states as the celiac syndrome. It seems that in spite of the improvement in knowledge of infant feeding and a wide dissemination among the members of the medical profession of this knowledge and in spite of the improvement in the quality and availability of the materials for feeding of infants problems of malnutrition will persist until the underlying disturbances in digestive and nutritional processes as related to disease are better understood. Therefore, it might be pertinent to inquire not only regarding the effects of nutrition in producing disease in infants but rather more concerning the effects of disease on nutrition. One may take the stand that the removal of the underlying disease or infection is all that is necessary. It is true that if this is done the nutritional problem seldom persists and the infant

From the Department of Pediatrics and Communicable Diseases, University of Michigan Medical School.

1. Jacobi, A.: Collectanea Jacobi, edited by William J. Robinson, New York, Critic and Guide Company, 1909, vol. 2, p. 93.

2. McKhann, C. F.: Failure of Infants to Gain Weight, Clinics **2**:274, 1943.

often promptly begins to gain weight. However, the removal or cure of an underlying disease may be impossible or may be dependent in whole or in part on an improvement in the nutritional status.

Malnutrition as an effect of disease may be brought about by one or more of several conditions: (1) the presence of anorexia, vomiting or diarrhea; (2) interference with digestion by diminution of gastrointestinal functions resulting in lessened gastric acidity, by decreased secretion of bile salts or by decreased secretion of enzymes; (3) interference with absorption of nutriment; (4) interference with utilization of nutriment; (5) augmented nutritional requirements due to increased metabolism and increased rate of utilization, and (6) increased rate of loss from the body.

Although refusal of food by and anorexia in ill infants is of common occurrence, the physiologic basis is not understood. The mechanism by which anorexia and vomiting induce loss of weight or failure to gain is obvious, since the foods do not enter or are lost from the gastrointestinal tract before the body has a chance to digest or to utilize them. The same may be said, perhaps to a lesser extent, in the case of diarrhea. Disturbed gastrointestinal function has been noted in patients having varied disease processes. One evidence frequently encountered has been diminished gastric acidity.[3] Faber noted achlorhydria associated with such infectious diseases as typhoid, malaria and pulmonary tuberculosis. Bloch found achylia gastrica after such infections as influenza, pneumonia or enteritis. More recently attention has been directed to interference in certain disease processes with the secretion of enzymes, chiefly those of the pancreas. Davison,[4] Stroe, Stroe and Théodorini [5] and Andersen [6] have shown a decrease of pancreatic enzymes in patients with diarrheas, both acute and chronic, and the last author has also demonstrated the decrease in patients with cystic fibrosis of the pancreas. Data on absorption of food substances are particularly lacking except in certain disease entities, such as the celiac syndrome, in which the absorption mechanism has been more carefully studied. Yet even in this condition the basic abnormality is still not clearly understood. Since the fundamental knowledge of utilization of foods is still incomplete, the effects of disease on utilization cannot be clearly defined. That an increase in rate of metabolism in such conditions as hyperpyrexia or hyperthyroidism will affect nutrition by increased utilization is evident. However, the factors responsible for increased rate of loss of essential nutritive substances from the body need further study.

The knowledge that malnutrition in infancy as seen today in the United States appears to result chiefly from effects of disease has led us to study and to attempt to analyze more thoroughly the various effects of disease on digestion, absorption and utilization of foodstuffs.

In this paper the effects of disease processes on absorption and utilization of vitamin A are reviewed.

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3. (*a*) Bloomfield, A. L., and Polland, W. S.: Gastric Anacidity: Its Relation to Disease, New York, The Macmillan Company, 1933. (*b*) Faber, K.: Etiology of Gastric Achylia, Arch. d. mal. de l'app. digestif **10**:641, 1920. (*c*) Bloch, C. E.: Chronic Dyspepsia in Young Children, Ugesk. f. læger **85**:1, 1923.

4. Davison, W. C.: (*a*) Duodenal Contents of Infants in Health, and During and Following Diarrhea, Am. J. Dis. Child. **29**:743 (June) 1925; (*b*) Enzymic Therapy in Infant Feeding, J. Pediat. **21**:727, 1942.

5. Stroe, S.; Stroe, H., and Théodorini, P.: Les ferments pancréatiques au cours des troubles digestifs de la première enfance, Nourrisson **17**:193, 1929.

6. Andersen, D. H.: Pancreatic Enzymes in the Duodenal Juice in the Celiac Syndrome, Am. J. Dis. Child. **63**:643 (April) 1942.

DETERMINATION OF VITAMIN A

Vitamin A is a fat-soluble organic compound, the exact structure of which is not established. At present at least two compounds exhibiting the activity of vitamin A are known to exist. The empiric formula is $C_{20}H_{30}O$.[7] Vitamin A is believed to be a degradation of the carotenoids. The liver appears able to convert carotenoids into vitamin A. In the body, the vitamin is stored chiefly in the liver; lesser amounts appear in the subcutaneous fat, adrenal cortex, corpus luteum and lutein cells of the ovary, with traces in the kidneys and lungs. Although it is present in sites of storage as the ester,[8] in the blood it appears chiefly as the free form. Both the provitamin and vitamin A are readily metabolized and in the normal human being are not excreted by the kidneys.[9]

The reaction described by Carr and Price[10] in 1926 is employed in most of the current methods of vitamin A assay.[11] Confusion occurs, however, because the results of vitamin A determinations are expressed in six or more different types of units (table 1). In this review values cited from reports of other authors will be expressed in the terms used by those authors (the international and the U. S. P. unit are equivalent).

Clausen and McCoord[11a] and Lewis, Bodansky and Haig[12] have demonstrated that there is little variation among blood levels in infants, children and adults.

TABLE 1.—*Normal Values of Blood Vitamin A*

	Type of Unit	Range per 100 Cc.	Mean	Age Group
Clausen and McCoord[11a]	Blue	10- 20	20	Children
May and others[11c]	Lese	5- 25	..	Children
Lewis and others[12]	U. S. P.	70-197	117	Children
Haig and Patek*	International	100-300	198	Adults
Murrill and others[11e]	Micrograms	20- 43	32	Adults
Present study	Micrograms	15- 40	..	Children

* Haig, C., and Patek, A. J., Jr.: Vitamin A Deficiency in Laennec's Cirrhosis, J. Clin. Investigation **21**:309, 1942.

May and associates[11c] have shown that for any person there is little diurnal or day to day variation and that though there is a wide range in normal values it is not a source of confusion, as the alteration in vitamin A and carotenoids in pathologic states is well beyond the limits found in normal circumstances.

7. Karrer, P.; Morf, R., and Schopp, K.: Zur Kenntnis des Vitamins A aus Fischtranen II, Helvet. chim. acta **14**:1431, 1931.

8. Gray, E. LeB.; Hickman, K. C. D., and Brown, E. F.: The State of Vitamin A in the Liver of the Rat After Feeding Various Forms of the Vitamin, J. Nutrition **19**:39, 1940.

9. The Vitamins: A Symposium Arranged Under the Auspices of the Council on Pharmacy and Chemistry and the Council on Foods of the American Medical Association, Chicago, American Medical Association Press, 1939. Rosenberg, H. R.: Chemistry and Physiology of the Vitamins, New York, Interscience Publishers, Inc., 1942.

10. Carr, F. H., and Price, E. A.: Color Reaction Attributed to Vitamin A, Biochem. J. **20**:498, 1926.

11. (*a*) Clausen, S. W., and McCoord, A. B.: The Carotinoids and Vitamin A of the Blood, J. Pediat. **13**:635, 1938. (*b*) Dann, J. W., and Evelyn, K. A.: The Determination of Vitamin A with the Photoelectric Colorimeter, Biochem. J. **32**:1008, 1938. (*c*) May, C. D.; Blackfan, K. D.; McCreary, J. F., and Allen, F. H., Jr.: Clinical Studies of Vitamin A in Infants and Children, Am. J. Dis. Child. **59**:1167 (June) 1940. (*d*) Kimble, M. S.: The Photocolorimetric Determination of Vitamin A and Carotene in Human Plasma, J. Lab. & Clin. Med. **24**:1055, 1939. (*e*) Murrill, W. A.; Horton, P. B.; Leiberman, E., and Newburgh, L. H.: Vitamin A and Carotene, J. Clin. Investigation **20**:395, 1941.

12. Lewis, J. M.; Bodansky, O., and Haig, C.: Level of Vitamin A in the Blood as an Index of Vitamin A Deficiency in Infants and in Children, Am. J. Dis. Child. **62**:1129 (Dec.) 1941.

ABSORPTION OF VITAMIN A

According to Drummond, Bell and Palmer,[13] who studied the absorption of vitamin A and carotene in a patient with a fistula of the thoracic duct which opened into the pleural cavity, analyses of the chylous fluid of the chest showed it to contain nearly all of the vitamin A ingested. The vitamin administered as the free alcohol or as the ester was found in lymph mainly as the ester. It appeared that absorption of vitamin A might depend on linkage with fatty acids in the intestinal wall. Carotene, a nitrogen-free aliphatic methylated polyene, does not undergo the same linkage with fatty acids, and the method of absorption should be different. In their study carotene was demonstrable only in small amounts in the chylous fluid.

Although the fat content of the diet does not seem to influence materially the absorption of vitamin A in normal human beings, the type of fat or oil ingested with the vitamin has some effect. Better absorption is obtained from vehicles of unsaturated oils, while administration of nonabsorbable oil, such as liquid petrolatum, decreases the absorption.[14] In pathologic states in which absorption of fat is quantitatively diminished, we have noted that a decrease in fat ingested allows for increase in absorption of vitamin A. Russell and associates,[15] studying hens, and Ahmad,[16] studying human beings, found that absorption of carotene is improved by the presence of fat in the diet and decreased by its absence. Thus, it appears that absorption of carotene also is linked with that of fat.

Studies of absorption of vitamin A have been facilitated by methods permitting determinations on the blood before and after oral administration of a test dose. Chesney and McCoord[17] in 1934 first reported a study of absorption of vitamin A in normal and in pathologic states. They demonstrated a peak of absorption in normal subjects between three and five hours after oral administration of vitamin A. This finding has been confirmed by Breese and McCoord[18] and by May and McCreary.[19] Breese and McCoord, using a test dose of 7,000 U. S. P. units of vitamin A per kilogram, demonstrated a rise of more than 100 units above pretest level, and May and McCreary, using 0.1 cc. of percomorph liver oil per pound (0.5 Kg.), showed an average rise of 130 L_{620} units. We have used a test dose of 5,000 U. S. P. units of vitamin A per pound (maximum dose 240,000 units) and have recorded only the value obtained four hours after the oral administration of the test dose. In normal subjects the average rise has been greater than 100 micrograms per hundred cubic centimeters.

Consideration of the chemical nature and the mode of absorption of vitamin A led investigators early to anticipate a decrease of absorption in conditions associated

13. Drummond, J. C.; Bell, M. E., and Palmer, E. T.: Observation on Absorption of Carotene and Vitamin A, Brit. M. J. **1**:1208, 1935.

14. Clausen, S. W.: The Pharmacology and Therapeutics of Vitamin A, J. A. M. A. **111**:144 (July 9) 1938.

15. Russell, W. C.; Taylor, M. W.; Walker, H. A., and Polskin, L. J.: The Absorption and Retention of Carotene and Vitamin A by Hens on Normal and Low Fat Rations, J. Nutrition **24**:199, 1942.

16. Ahmad, B.: The Fate of Carotene After Absorption in the Animal Organism, Biochem. J. **25**:1195, 1931.

17. Chesney, J., and McCoord, A. B.: Vitamin A of Serum Following Administration of Haliver Oil in Normal Children and in Chronic Steatorrhea, Proc. Soc. Exper. Biol. & Med. **31**:887, 1934.

18. Breese, B. B., Jr., and McCoord, A. B.: Vitamin A Absorption in Celiac Disease, J. Pediat. **15**:183, 1939.

19. May, C. D., and McCreary, J. F.: The Absorption of Vitamin A in Celiac Disease, J. Pediat. **18**:200, 1941.

with poor utilization of fat, such as obstructive jaundice, cystic fibrosis of the pancreas and the celiac syndrome.

JAUNDICE

As early as 1855 keratomalacia was noted in association with jaundice. However, not until the cause of keratomalacia was known could controlled studies be made. Bloch [20] first reported a case of jaundice in which xerosis and arrested growth persisted despite oral administration of cod liver oil. When the feces became bile stained and the jaundice disappeared, the xerosis gradually cleared and the child began to grow. Blegvad [21] in 1923 reported a case of xerophthalmia in a patient who had cancer of the head of the pancreas with obstructive jaundice in which the xerosis disappeared after subcutaneous injection of cod liver oil concentrates. That the exclusion of bile may be responsible for lack of absorption of vitamin A was further pointed out by Altschule,[22] who reported vitamin A deficiency at necropsy in 11 of 60 infants who had adequate intake of vitamin A but who suffered from congenital atresia of the bile ducts. In reviewing the subject

TABLE 2.—*Absorption of Vitamin A in Patients with Obstructive Jaundice*

Patient	Diagnosis	Vitamin A Absorption Test Rise Above Pretest Level
J. S.	Obstructive jaundice secondary to inspissation within biliary passage...	0.0
S. C.	Congenital atresia of bile ducts.....	0.2 Lese units
J. P.	Congenital atresia of bile ducts.....	0.0
S. E.	Congenital atresia of bile ducts.....	8.9 micrograms per 100 cc.

TABLE 3.—*Absorption of Vitamin A in Obstructive Jaundice When Bile Salts Are Mixed with Test Dose*

Test Dose, 5,000 U. S. P. Units per Pound	Fasting Level Vitamin A, Micrograms per 100 Cc.	Vitamin A Blood Level Four Hours after Ingestion of Test Dose, Micrograms per 100 Cc.
(1) Vitamin A concentrate.....	0.84	9.7
(2) Vitamin A concentrate administered as emulsion with bile salts	17.8	102.6

he noted that in 1851 it had been reported that keratomalacia occurred in 2 dogs with biliary fistulas. Greaves and Schmidt [23] in 1935, working with choledochocolonostomized rats, showed that carotene given orally failed to be absorbed. In their experiments, vitamin A was absorbed but carotene was absorbed only when administered with bile salts. For human beings there are adequate studies to show that vitamin A as well as carotene is not absorbed in the absence of bile salts. Breese and McCoord [24] in 1940 reported that patients with catarrhal jaundice absorbed vitamin A poorly and that improvement in absorption paralleled the improvement in the disease. It was their impression that bile salts given orally probably aided

20. Bloch, C. E.: Further Clinical Investigation into the Diseases Arising in Consequence of a Deficiency in the Fat Soluble A Factor, Am. J. Dis. Child. **28**:659 (Dec.) 1924.

21. Blegvad, O.: Treatment of Xerophthalmia, Ugesk. f. læger **85**:942, 1923.

22. Altschule, M. D.: Vitamin A Deficiency in Spite of Adequate Diet in Congenital Atresia of Bile Ducts and Jaundice, Arch. Path. **20**:845 (Dec.) 1935.

23. Greaves, J. D., and Schmidt, C. L. A.: On Absorption and Utilization of Carotene and Vitamin A in Choledochocolonostomized Vitamin A Deficient Rats, Am. J. Physiol. **111**:492, 1935.

24. Breese, B. B., and McCoord, A. B.: Vitamin A Absorption in Catarrhal Jaundice, J. Pediat. **16**:139, 1940.

the absorption. May and McCreary [19] in 1941 found almost complete absence of absorption of vitamin A in 3 infants with congenital atresia of bile ducts. Table 2 presents illustrative results from our studies.

In order to prove that lack of absorption was due to absence of bile salts in the last patient, S. E., with congenital atresia proved by operation, the absorption test was repeated, with vitamin A in a mixture with bile salts used as the test dose (table 3).

From the available data it would seem that the absence of bile salts in obstructive jaundice is a large factor in the interference with absorption of vitamin A.

CYSTIC FIBROSIS OF PANCREAS

Cystic fibrosis of the pancreas seems to represent a condition in which pancreatic secretions fail to reach the intestine. The exclusion of pancreatic enzymes interferes with digestion and absorption of fat and of vitamin A. The decrease in absorption of vitamin A in patients with this disease was pointed out by Blackfan and May [25] in 1938, by Breese and McCoord [18] in 1939 and by May and co-workers [11c] in 1940. Andersen,[26] who reviewed the subject in 1938, expressed the opinion that cystic fibrosis is congenital in origin. Blackfan and Wolbach [27] suggested that the pathogenesis resided in the production of an abnormal pancreatic secretion which inspissated and led to distention and atrophy of the ducts.

Until one determines whether mixtures of pancreatin and vitamin A allow for normal absorption of vitamin A as mixtures of vitamin A and bile salts did in the case of obstructive jaundice, one cannot be certain that the defect is primarily in the pancreas, as suggested by Andersen, and not a primary disturbance of absorption of fat with secondary pancreatic changes. The differentiation of cystic fibrosis of the pancreas from the celiac syndrome is not always easy, and in a number of instances the diagnosis of cystic fibrosis of the pancreas has had to be changed to celiac syndrome, and vice versa. It would seem that the possibility that both conditions represent degrees of severity of the same process should not be entirely dismissed.

CELIAC SYNDROME

The celiac syndrome represents a chronic disturbance in nutrition in childhood in which there are defective motility of the intestinal tract and defective absorption of fats and carbohydrates. May, McCreary and Blackfan [28] desired that the term "syndrome" be reserved for disturbances secondary to such disorders as chronic infection of the lungs, ears or urinary tract, dysentery, tuberculosis and disorders of the pancreas and that the term "celiac disease" be used only when there is no other disease process present. As regards the cause of celiac disease, these authors discussed the factors involved in the absorption of fat and by exclusion concluded that the defect in the ability of the intestinal mucosa to absorb vitamin A, and presumably fat, is due to a lack of some intrinsic or extrinsic

25. Blackfan, K. D., and May, C. D.: Inspissation of Secretion, Dilation of the Ducts and Acini, Atrophy and Fibrosis of the Pancreas, J. Pediat. **13**:627, 1938.

26. Andersen, D. H.: (*a*) Cystic Fibrosis of the Pancreas and Its Relation to Celiac Disease, Am. J. Dis. Child. **56**:344 (Aug.) 1938; (*b*) Cystic Fibrosis of the Pancreas, Vitamin A Deficiency and Bronchiectasis, J. Pediat. **15**:763, 1939.

27. Blackfan, K. D., and Wolbach, S. B.: Vitamin A Deficiency in Infants: Clinical and Pathological Study, J. Pediat. **3**:679, 1933.

28. May, C. D.; McCreary, J. F., and Blackfan, K. D.: Notes Concerning the Cause and Treatment of Celiac Disease, J. Pediat. **21**:289, 1942.

substance; this therefore places celiac disease in the category of a deficiency state. In support of this view, the improvement that occurred in 11 cases after the daily parenteral administration for a period of three to six weeks of large amounts of vitamin B complex and crude liver extract is cited. If celiac disease does represent a deficiency in one of the factors of the B complex, the question arises as to how the deficiency occurs, since there is usually no history of dietary inadequacy of the B vitamins. An unrecognized influence which affects utilization by the intestinal mucosa of some portion of the vitamin B complex would therefore be responsible.

It is interesting to note that in their cases of "celiac syndrome" the administration of vitamin B complex and liver extract had no effect. The mechanism whereby a chronic infection like otitis media without evidence of pathologic changes in the gastrointestinal tract could produce the picture of celiac disease needs further clarification. To emphasize the prevailing ignorance of the underlying mechanism promoting absorption of fat, Adlersberg and Sobotka [29] demonstrated in patients with sprue, a condition somewhat similar to celiac disease, striking improvement in the absorption of fat and of vitamin A by the addition of lecithin to the test dose. Another factor, not so far alluded to, which may produce the clinical picture of celiac disease is gastrointestinal allergy.[30] In any event, in both the syndrome and the disease with the defect in absorption of fat, there is an associated failure in absorption of vitamin A. The absorption is so constantly diminished that it has been proposed as one of the criteria in the diagnosis and as a guide to recovery.

INFECTION

Infection, in our previous study the most important single cause of malnutrition in infancy, appears also to be an important factor in the production of abnormality in absorption and utilization of vitamin A in human beings.

Although "fat-soluble A" in cod liver oil and in butter was not described as a specific substance until 1914, keratomalacia, subsequently shown to be a vitamin A deficiency state, had been known for many years. As early as the middle of the nineteenth century keratomalacia had been noted to be associated not only with poor diets but with certain disease states, such as jaundice and debilitating infections. Thompson [31] in 1894, reporting a case of keratomalacia in a 2 month old child who had severe jaundice, stated: "Amongst the causes of keratomalacia as generally accepted are infantile diarrhea, measles, whooping cough, encephalitis, starvation, or ill-advised feeding of infants." Blegvad,[32] in reviewing the subject of xerophthalmia in 1924, noted that many authors had observed keratomalacia in association with diseases of the digestive organs and also in patients with measles, scarlatina, typhus, dysentery, cholera, tuberculosis, influenza, variola and icterus. However, the earlier reports contain no reference to the diet of the patients, and therefore conclusions cannot be drawn as to whether the deficiency in the reported diseases represented a lack of intake of vitamin A or a lack of absorption or utilization of vitamin A. Until Bloch in 1917 showed that keratomalacia was associated with a deficiency of a fat-soluble A factor, controlled observations could

29. Adlersberg, D., and Sobotka, H.: Influence of Lecithin Feeding on Fat and Vitamin A Absorption in Man, J. Nutrition **25**:255, 1943.

30. McKhann, C. F.; Spector, S., and Meserve, E. R.: An Association of Gastrointestinal Allergy with the Celiac Syndrome, J. Pediat. **22**:362, 1943.

31. Thompson, J. T.: Keratomalacia in Acute Infantile Jaundice, Brit. M. J. **2**:597, 1894.

32. Blegvad, O.: Xerophthalmia, Keratomalacia and Xerosis Conjunctivae, Am. J. Ophth. **7**:89, 1924.

not be made. In 1920 he [33] concluded that there are three etiologic factors responsible for the origin and development of xerophthalmia. "Firstly, the diet which does not contain or at any rate is poor in the specific lipoid body or bodies. Secondly, growth; xerophthalmia is found particularly in children or animals who are growing. Thirdly, antecedent infections of long duration." In 1924, in answer to his critics who cited cases in which despite diets adequate in fats xerophthalmia occurred, Bloch stated: "The organism's lack of the fat-soluble A factor of which xerophthalmia is the characteristic symptom must therefore arise partly from a deficient supply, that is, food poor in fat-soluble A factor, or diseases of the intestinal tract which hinder digestion and absorption of this factor, and partly from increased consumption during the periods of growth and in wasting infections."

In 1933 Clausen,[34] discussing the exploitation of vitamin A, noted that in a study of 1,322 children in only 5 per cent could one possibly consider that lowering of carotenoids was responsible for infection; and, in fact, it was his opinion that fall of carotenoids did not precede infection but resulted from it. In another paper [35] he demonstrated that children with infections had a fall in plasma carotenoids which in general corresponded with the severity of the infection, this despite normal intake of carotene. In his conclusion he stated that "it will be evident that a low level of carotinoids cannot be considered as preceding, or predisposing to, the infections; but rather as a consequence of the infection. This lowering may be due to any of three causes: (1) more rapid utilization in fever, (2) slower absorption and (3) poor appetite." [34]

Thus, the fact that infection alters the absorption or utilization of vitamin A has been known for many years. However, it is only in the last decade, since methods have been available permitting more adequate determinations of vitamin A, that it has been possible to investigate the mechanism by which infection tends to produce the vitamin A deficiency state.

Absorption of Vitamin A in Infection.—During infections there develops rather regularly a decrease in the ability of the intestinal tract to absorb carotene and vitamin A. The decreased absorptive power occurs even with infections that do not primarily involve the gastrointestinal tract and in which there are no apparent associated gastrointestinal symptoms.

Clausen [35] in 1934 reported a study of absorption of carotene in oil in patients with scarlet fever. In the first week of the illness the blood level of carotenoids continued to fall despite the daily administration of carotene, and it was only after the seventh day in patients with uncomplicated scarlet fever that carotene began to rise. In patients with complications the rise did not occur until the tenth day (chart). The rise in carotenoids, when it did occur, was accompanied by a rise in vitamin A; this indicates that the ability of the liver to convert carotene into vitamin A remained intact. That the failure of plasma carotenoids to increase represented a failure of absorption was intimated by close parallelism between the curve produced by rate of fall during the first week of scarlet fever and that occurring in healthy children on a carotene-free diet.

Heymann [36] in 1934, measuring fecal output of an ingested amount of carotene in oil, was able to determine that healthy infants 2 to 12 months of age absorbed

33. Bloch, C. E.: Clinical Investigations of Xerophthalmia and Dystrophy in Infants and Children, J. Hyg. **19**:283, 1921.

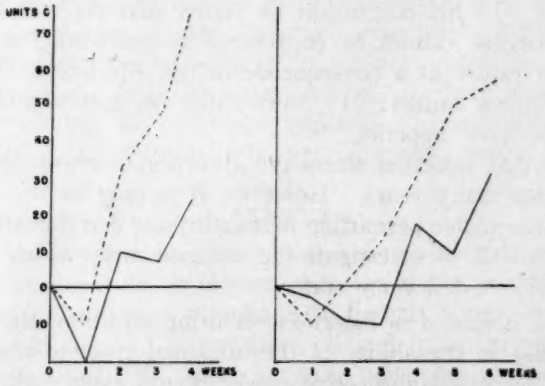
34. Clausen, S. W.: Limits of the Anti-Infective Value of Provitamin A, J. A. M. A. **101**:1384 (Oct. 28) 1933.

35. Clausen, S. W.: The Exploitation of Vitamin A, New York State J. Med. **34**:154, 1934.

36. Heymann, W.: Absorption of Carotene, Am. J. Dis. Child. **51**:273 (Feb.) 1936.

about 70 per cent. He then studied 18 infants—4 with pneumonia, 12 with grip and 1 with sepsis—and showed that the absorption was diminished, averaging only 35 per cent. The disturbance in absorption persisted for as long as two weeks after the fall of temperature to normal. As another evidence that the greatly diminished rate of absorption was not attributable to the fever, he could demonstrate no fall of the carotene when the fever was induced by vaccinia. In his patients he showed that there was no accompanying decrease in the absorption of total fat. However, he did show that when there was a disturbance in the absorption of fat, as in celiac disease, the carotene also failed to be absorbed. The thought must recur that the celiac syndrome may represent an advanced effect of infection or a similar disease process on the intestinal tract, producing difficulty in absorption not only of vitamin A but of fats as well. Further credence may be given this when it is noted that May listed 4 cases of celiac syndrome secondary to chronic otitis media and 1 secondary to chronic pyelonephritis.[37]

Clausen [14] in 1938, in a review of the pharmacology and therapeutic effectiveness of vitamin A, stated that vitamin A is poorly absorbed during infections.



Increase of carotenoids above the initial level in scarlet fever. The figure at the left presents results for 25 patients in whom the disease was not complicated at the onset; the broken line represents values for 11 patients who received carotene and the solid line values for 14 who did not receive carotene. The figure at the right presents results for 22 patients in whom the disease was complicated at the onset; the broken line represents values for 14 patients who received carotene and the solid line values for 8 who did not receive supplementary carotene (after Clausen [25]).

May and McCreary [19] in 1941, in discussing other conditions besides celiac disease which interfere with absorption of vitamin A, listed 2 cases of pneumonia. Breese, Watkins and McCoord [38] in 1942 reported a study of absorption of vitamin A in 29 patients with severe pulmonary tuberculosis. The absorption by these patients was poorer than that obtaining in normal persons; on the average, the more severe the malnutrition, the poorer was the ability to absorb vitamin A. They further noted that in those patients coming to necropsy there were no gross or microscopic pathologic changes demonstrable in the intestines which could explain the lack of absorption. We, too, have found that infections, even though unassociated

37. Presupposing that lack of absorption of fat may be a result of lack of phosphorylation because of some deficiency factor in the vitamin B complex, investigations are now being made concerning the effect of infection on absorption and utilization of vitamin B.

38. Breese, B. B., Jr.; Watkins, F., and McCoord, A. B.: The Absorption of Vitamin A in Tuberculosis, J. A. M. A. **119**:3 (May 2) 1942.

with fever or with gastrointestinal symptoms, may cause a decrease in the ability of the patient to absorb vitamin A.

Among the acute infections in which a decrease in absorption of vitamin A occurred have been scarlet fever, measles and pneumonia. The duration of the defective absorption in these conditions has been relatively short. The cases in table 4 may be cited as examples.

The similarity in degree of absorption of vitamin A in patient R. S. during the course of scarlet fever to that found in subjects reported on by Clausen when carotene was used is interesting.

However, acute infection does not rank high among the causes of malnutrition, and any influence of acute infection on absorption of vitamin A is probably of too short duration to be of clinical significance, especially in a patient on a previously

Table 4.—*Absorption of Vitamin A in Patients with Acute Infections*

Patient	Age, Yr.	Diagnosis	Comment	Fasting Blood Level of Vitamin A, Micrograms per 100 Cc.	Level 4 Hr. After Ingestion of Test Dose, Micrograms per 100 Cc.
R. S.	14	Scarlet fever	3d day of illness, temp. 100 F.	20.6	31.1
			5th day, afebrile	20.3	71.0
			7th day, afebrile	32.3	44.4
			9th day, afebrile	11.3	51.3
			11th day, afebrile	28.4	114.0
			14th day, afebrile	34.6	115.7
			16th day, afebrile	56.0	71.3
			19th day, afebrile	37.0	70.0
			22d day, afebrile	32.6	64.9
W. C.	21	Scarlet fever	5th day, afebrile and asymptomatic	19.0	17.8
			14th day, asymptomatic	32.2	32.8
E. B.	26	Scarlet fever	7th day, temp. 103 F.	8.6	32.0
			10th day, temp. 101 F.	16.8	78.2
			19th day, asymptomatic	27.6	77.2
M. B.	6	Typhoid	19th day, temp. 103 F.	4.6	6.2
J. B.	8	Typhoid	19th day, temp. 102 F.	14.0	18.6
H. H.	19	Scarlet fever	20th day, asymptomatic	64.0	177.0
G. B.	10	Measles	2d day of rash, temp. 103 F.	21.2	24.0
			8th day, afebrile	45.3	91.8
			1 month later	37.5	236.0
C. B.	15	Measles	2d day of rash	13.9	31.8
J. O.	24	Measles	4th day of rash, afebrile	26.9	371.0
J. P.	5	Pneumonia	Fever, rapid respirations	12.0	12.0
			Afebrile 3 days	24.6	72.5

good diet. More consideration should be given to subacute or chronic infections, which play important roles in production of malnutrition and in which defective intestinal absorption would be of prolonged duration. One such condition is infection of the upper respiratory tract associated with postnasal discharge. A case history may be especially illuminative.

C. O., an 11 month old white boy, was admitted to the hospital because of loss of weight and vomiting. The birth and developmental history were normal. At the age of 5 months he had an infection of the upper respiratory tract characterized by a thick mucopurulent nasal discharge. Associated with this infection, vomiting became pronounced, occurring soon after feedings and being projectile. The nasal discharge and vomiting persisted despite several courses of chemotherapy. During a period of six months the baby's weight fell from 19 pounds (8,620 Gm.), which he had attained at 5 months of age, to 13 pounds (5,900 Gm.). On admission he was slightly underdeveloped and seriously malnourished despite being offered a good diet with ample vitamin supplements. His height was 26½ inches (67 cm.); his weight was 13 pounds (5,900 Gm.), and his temperature was 99.2 F. rectally. Abnormal conditions observed were a mucopurulent postnasal discharge and costochondral beading suggestive of scurvy. Examination of the blood revealed a hemoglobin content of 46 per cent, a red cell count of 2,800,000 and a white cell count of 7,100, with a normal differential distribution. The Kahn reaction of the blood was negative. A tuberculin test elicited a negative response.

The urine was normal. A roentgenogram of the chest disclosed no abnormality; that of the bones revealed mild but definite scurvy, and those of the gastrointestinal tract showed normal pattern and motility. Gastric analysis showed no free hydrochloric acid and only a minimal response to oral administration of 10 per cent alcohol. The dextrose tolerance curve was flat. The fasting level of dextrose was 91 mg. per hundred cubic centimeters; at the end of one-half hour after ingestion of the test dose it was 91 mg.; at the end of one hour, 92 mg.; at the end of two hours, 95 mg., and at the end of three hours, 97 mg. A test of absorption of vitamin A revealed a fasting level of 11.3 micrograms per hundred cubic centimeters, which rose only 2 micrograms four hours after the test dose. The plasma level of the ascorbic acid was 0.3 mg. per hundred cubic centimeters; after the boy had received 50 mg. of ascorbic acid three times a day for a period of two weeks, the blood level remained 0.3 mg. per hundred cubic centimeters. Symptomatic treatment failed to induce improvement in the nasal infection. The child's hemoglobin content rose with transfusion and iron therapy to 80 per cent, and the elimination of scurvy followed parenteral administration of ascorbic acid. The child was afebrile; yet, despite a diet of lactic acid evaporated milk of 68 calories per pound (150 calories

TABLE 5.—*Absorption of Vitamin A in Patients with Chronic Infection*

Patient	Age, Yr.	Diagnosis	Comment	Fasting Blood Level of Vitamin A, Micrograms per 100 Cc.	Level 4 Hr. After Ingestion of Test Dose, Micrograms per 100 Cc.
H. G.	12	Chronic pansinusitis	Afebrile	26.2	35.1
W. C.	9/12	Chronic pneumonitis	Malnutrition	15.6	38.0
E. B.	13	Bilateral bronchiectasis	Afebrile	29.5	25.0
H. R.	10	Bilateral bronchiectasis	Afebrile	21.0	19.7
			After 2 weeks of postural drainage	29.5	46.3
A. C.	11	Chronic osteomyelitis	Afebrile	11.1	9.8
P. M.	2	Tuberculous meningitis	.....	13.6	24.0

TABLE 6.—*Absorption of Vitamin A in Control Patients*

Patient	Age, Yr.	Diagnosis	Fasting Blood Level of Vitamin A, Micrograms per 100 Cc.	Level 4 Hr. After Ingestion of Test Dose, Micrograms per 100 Cc.
R. W.	5/12	Convulsive disorder	39.8	159.5
B. C.	2	Cleft palate	19.0	193.0
B. K.	3	Osteogenesis imperfecta	24.0	95.0
J. W.	3	Congenital ichthyosis	14.9	144.0
J. T.	5	Cardiospasm	33.2	256.0
M. H.	8	Diabetes mellitus	34.4	429.0
R. R.	10	Myopia	25.8	141.0
F. D.	12	Congenital syphilis	32.0	135.0

per kilogram) and vitamin A, B, C and D supplements, the patient in a period of one month's observation failed to gain weight. At the end of this time an adenoidectomy was performed, which rid the child of the chronic infection in the posterior part of the nasopharynx. In six days he gained more than 1 pound (454 Gm.) and the vitamin A absorption test showed a rise of absorption of 65.0 micrograms per hundred cubic centimeters in contrast to the previous rise of 2.0 micrograms. Two months after his discharge from the hospital the child returned and was found to weigh 19 pounds 4 ounces (8,730 Gm.), a gain of 5 pounds (2,270 Gm.). A dextrose tolerance curve at this time was completely normal. The blood level of vitamin C was 0.5 mg. per hundred cubic centimeters, and vitamin A absorption, although present, was still impaired.

This case would seem to typify the important role infection may play in absorption of dextrose and fat and vitamins A and C.

In patients with other chronic infections, such as chronic sinusitis, pneumonitis, bronchiectasis, osteomyelitis, rheumatic fever and tuberculosis, defect in absorption of vitamin A was also demonstrable (table 5).

In contrast may be listed the values obtained in states in which absorption of vitamin A was not affected (table 6).

As regards failure of absorption of vitamin A in the presence of infection, it should be pointed out that May and Lewis as well as we have previously shown that despite the failure of the plasma level of vitamin A to rise during an absorption test supplementary vitamin A given orally, preferably as a concentrate and in divided doses during the day, usually allows for enough absorption to prevent the development of a deficiency state. In those conditions in which there is also an associated difficulty in absorption of fats, the absorption of vitamin A given as outlined may be further enhanced if the diet given is low in fat.

Excretion of Vitamin A in Patients with Infection.—In normal human beings there seems to be no urinary excretion of vitamin A.[39] However, in certain pathologic states vitamin A may be excreted in the urine. The mechanism of this is not understood, although Lawrie, Moore and Rajogapol [39c] found that in the urine the vitamin was associated with a non-heat-coagulable protein and that in these states the urine reacted positively for proteose, peptone, trypsin, tryptophan and arginine and also differed from normal urine in its ability to take up more vitamin A in a form sufficiently dispersed to pass through a wet filter paper. The excretion appeared to be selective, as the concentration of vitamin A per unit of lipid was much greater in the urine than in the blood.

The pathologic state which was most often accompanied by abnormal excretion was pneumonia. Lindqvist [40] in 1937 reported that the excretion in pneumonia varied from 228 to 3,060 international units daily before the crisis, falling to zero after the crisis. Boller and Brunner [41] in 1937 noted the presence of vitamin A in the urine of patients with lobar pneumonia before the crisis, and in patients with chronic nephritis, nephrosis, cirrhosis of the liver and obstructive jaundice. Hedberg and Lindqvist [42] in 1938 also called attention to the increased excretion of vitamin A in chronic nephritis and noted that it was associated with a high blood level and a low reserve in the liver. Lawrie, Moore and Rajogopal [39c] in 1941 showed urinary excretion of 6 to 480 international units per hundred cubic centimeters in 15 of 17 patients with pneumonia before the crisis; of 3 and 68 international units in 2 of 3 patients with empyema; of 15 international units in 1 of 2 persons with asthma and of 12 to 52 international units in 6 of 10 patients with chronic nephritis. In a group of 45 patients with miscellaneous diseases, such as rheumatic fever, arthritis, diabetes and tuberculosis, there were only 4 instances of urinary excretion of vitamin A. These authors emphasized, however, that the excretion of vitamin A in pneumonia was not enough to account fully for the fall of the vitamin A in the blood in that disease.

Vitamin A Storage in Infection.—Vitamin A when ingested in optimal doses or in amounts greater than that required for immediate use is stored chiefly in the liver in an esterified form. Ellison and Moore,[43] in a study of children who

39. (*a*) Rowntree, J. I.: A Study of the Absorption and Retention of Vitamin A in Young Children, J. Nutrition **3**:265, 1930. (*b*) Kauffmann, F., and von Drigalski, W.: Untersuchungen über Carotin-Vitamin A im menschlichen Organismus, Klin. Wchnschr. **12**:306, 1933. (*c*) Lawrie, N. R.; Moore, T., and Rajogopal, K. R.: Excretion of Vitamin A in the Urine, Biochem. J. **35**:825, 1941.

40. Lindqvist, T.: Untersuchungen über das Vitamin A bei Pneumonie, Klin. Wchnschr. **16**:1345, 1937.

41. Boller, R., and Brunner, O.: Ueber die Ausscheidung von Vitamin A im Harn, Klin. Wchnschr. **16**:861, 1937.

42. Hedberg, J., and Lindqvist, T.: Untersuchungen über das Vitamin A bei chronischen Nephriten, Acta med. Scandinav. (supp.) **90**:231, 1938.

43. Ellison, J. B., and Moore, T.: Vitamin A and Carotene: The Vitamin A Reserve of Human Infant and Child in Health and Disease, Biochem. J. **31**:165, 1937.

died by accident, determined that the mean hepatic content in childhood was 130 international units of vitamin A per gram. According to age, the content was as follows: birth to 4 weeks, 17 units per gram; 5 weeks to 3 months, 14 units, and 4 months to 14 years, 130 units. Wolff [44] reported that livers of newborn infants contained on the average 42 units per gram. Lewis, Bodansky and Haig found the average for 20 newborn infants to be 115 U. S. P. units. For adults, Moore [45] reported the average value to be 220 international units per gram. Crimm and Short [46] in 7 cases reported the average as 330 U. S. P. units per gram. Ralli [47] in 25 cases of accidental death had a range of vitamin A from 30 to 6,390 U. S. P. units per gram of liver, with an average of 760 units.

The manner in which vitamin A may be liberated from its stores is as yet unknown. Clausen and associates [48] used injections of epinephrine hydrochloride, histamine, insulin and mecholyl chloride, exsanguination, inhalations of chloroform and of ether and operative trauma without producing a rise in serum vitamin A. However, when alcohol was given there was a pronounced rise; the increase was chiefly of the esterified form of the vitamin. During the period of administration of alcohol, a decrease of vitamin A occurred in the hepatic stores in 2 of 3 dogs. That alcohol increased the rate of depletion of vitamin A from the liver was also noted by Baumann, Foster and Moore.[49] It is known that the

TABLE 7.—*Vitamin A Content of Liver in Diseases of Children* (*Ellison and Moore* [43])

Disease	Vitamin A Content of Liver, International Units per Gm.
None	130
Measles	110
Pneumonia	78
"Head infections"	68
Sepsis	47
Heart disease	50

TABLE 8.—*Vitamin A Content of Liver in Disease in Adults* (*Moore* [45])

Disease	Vitamin A Content of Liver, International Units per Gm.
None	220
Bronchiectasis and chronic bronchitis	80
Subacute nephritis	75
Peritonitis	75
Enteritis and colitis	74
Pneumonia	63
Valvular disease of the heart	60
Sepsis	51
Chronic nephritis	25

44. Wolff, L. K.: On the Quantity of Vitamin A Present in the Human Liver, Lancet **2**:617, 1932.

45. Moore, T.: Vitamin A and Carotene: The Vitamin A Reserve of the Adult Human Being in Health and Disease, Biochem. J. **31**:155, 1937.

46. Crimm, P. D., and Short, D. M.: Vitamin A Content of Human Liver in Tuberculosis, Ann. Int. Med. **13**:61, 1939.

47. Ralli, E. T.; Papper, E.; Paley, K., and Baumann, E.: Vitamin A and Carotene Contents in Normal and in Diseased Subjects: An Analysis of One Hundred and Sixteen Human Livers, Arch. Int. Med. **68**:102 (July) 1941.

48. Clausen, S. W.; Baum, W. S.; McCoord, A. B.; Rydeen, J. O., and Breese, B. B.: The Mobilization by Alcohols of Vitamin A from Its Stores in the Tissues, J. Nutrition **24**:1, 1942.

49. Baumann, C. A.; Foster, E. S., and Moore, P. R.: The Effects of Dibenzanthracene, of Alcohol, and of Other Agents on Vitamin A in the Rat, J. Biol. Chem. **142**:597, 1942.

stored vitamin A is used rapidly when the intake or absorption of food is inadequate. Also, one would expect that with increased destruction or utilization of vitamin A the stores in the liver would be depleted. Thus, it is interesting to look to the results of studies of the vitamin A content of the liver in disease. Clausen [34] in 1933 noted that in infections the hepatic content of vitamin A was reduced. The findings of Ellison and Moore [43] in a study of 200 children are listed in table 7.

A comparison of the reserves found at autopsy in 9 patients with measles treated with vitamin A concentrate and a group untreated showed almost no difference. Moore [45] in 1,000 autopsies on adults also noted a marked reduction of vitamin A storage in infections (table 8).

Ralli and co-workers,[47] stressing the role of the liver in deficiency of vitamin A, pointed out that the storage of vitamin A is affected greatly by processes or diseases which tend to produce pathologic changes in the liver (table 9).

Other conditions besides infection which are apt to decrease the vitamin A content of the liver are alcoholism and cirrhosis (as already shown), obstructive jaundice, celiac syndrome and hypothyroidism.

Blood Level of Vitamin A in Infection.—It has previously been shown that the blood level of vitamin A is fairly constant for any person and that the normal

TABLE 9.—*Vitamin A Content of Liver in Pathologic States (Ralli [47])*

Pathologic State	Liver Content of Vitamin A, U. S. P. Units per Gm.	Liver Content of Carotene, Mg. per 100 Gm.
None	700	1.36
Alcoholism	375	0.90
Cirrhosis	137	0.57
Chronic infection	380	0.79
Acute infection without hepatic damage	450	0.95
Acute infection with hepatic damage	240	0.45

range (table 1) although wide is no cause for confusion, as the alterations in pathologic states are fairly pronounced.

Lewis and co-workers [50] and Horton and others [51] have pointed out that the blood level of vitamin A in rats is an accurate index of hepatic storage and state of vitamin A nutrition. In human beings it has been demonstrated that the diminution of the blood level of vitamin A is the first evidence of vitamin A deficiency, especially of storage. However, the decrease may precede by a long period the onset of actual symptoms, the first of which is probably impaired dark adaptation. The appearance of cornification of normal epithelium is a late symptom and apparently takes months to manifest itself.

Clausen and McCoord [11a] in 1938 reported studies of the plasma values of the vitamin in three groups of children: (1) normal children; (2) children with mild or moderate infections, and (3) children with severe infections, such as pneumonia, mastoiditis, meningitis and septicemia (table 10). It was their opinion that the decrease in vitamin A in infection was due to a decrease in intake and to increased utilization because of the fever. In an effort to substantiate the second factor,

50. Lewis, J. M.; Bodansky, O.; Falk, K. G., and McGuire, G.: Relationship of Vitamin A Blood Level in the Rat to Vitamin A Intake and to Liver Storage, Proc. Soc. Exper. Biol. & Med. **46**:248, 1941.

51. (*a*) Horton, P. B.; Murrill, W. A., and Curtis, A. C.: Vitamin A and Carotene: I. The Determination of Vitamin A in the Blood as an Index of Vitamin A Nutrition of the Rat, J. Clin. Investigation **20**:287, 1941. (*b*) Meyer, K. A.; Popper, H.; Steigmann, F.; Walters, W. H., and Zevin, S.: Comparison of Vitamin A of Liver Biopsy Specimens with Plasma Vitamin A in Man, Proc. Soc. Exper. Biol. & Med. **49**:589, 1942.

they examined 19 patients who were exposed to artificial hyperthermia. A marked fall in blood level occurred in 17 of the 19 persons. This fall was most evident as a rule immediately after the completion of the treatment, and the lowest levels were found in persons having the lowest initial levels in vitamin A. In 6 instances the level of vitamin A increased above the initial level between the first and the third day after the onset of treatment. The rise after fever suggested to Clausen and McCoord liberation from stores, increased digestion due to improved appetite or temporary inability to store the vitamin as rapidly as normally.

Lindqvist [40] in 1937 pointed to a decrease in blood level of vitamin A in pneumonia from the normal of 70 to 27 international units per hundred cubic centimeters. Although this was associated with an abnormal excretion of 228 to 3,060 units per twenty-four hours in the urine before the crisis, the decrease could not be fully explained on that basis. Josephs [52] in 1943 has also noted a decrease of vitamin A in the blood in pneumonia and has shown that it is associated

TABLE 10.—*Blood Levels of Vitamin A in Normal Infants and in Infants with Mild and with Severe Infections (Clausen and McCoord [11a])*

Age	Normal, "Blue" Units	Mild or Moderate Infection, "Blue" Units	Severe Infection, "Blue" Units
Birth	12.8	....	....
0 to 6 months	23.8	15.0	9.1
6 to 24 months	19.9	12.9	9.5
2 years	20.2	15.1	6.8

TABLE 11.—*Level of Vitamin A in the Blood and Dark Adaptation of Children 6 to 12 Years of Age (Lewis, Bodansky and Haig [12])*

Group	Number of Children	Level of Vitamin A in Blood Plasma, U. S. P. Units per 100 Cc.		Number of Children with Abnormal Dark Adaptation
		Range	Average	
Normal	19	70-197	117	0
Afebrile	118	25-198	89	1
Febrile	20	10- 95	44	4

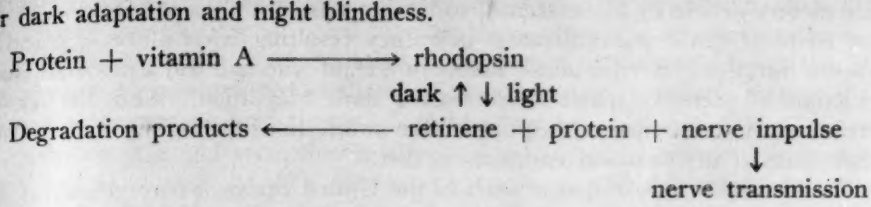
with a fall in blood lipids. Lindqvist showed that in chronic nephritis, in which there existed abnormal excretion, the blood level was elevated to 120 international units. However, in the latter condition there was an associated depletion of vitamin A in the liver.

Lewis, Bodansky and Haig [12] in 1941 determined the blood level of vitamin A and the dark adaptation of three groups of children: a normal group; an afebrile or miscellaneous group who had been admitted with disorders such as infection of the upper respiratory tract, rheumatic fever, dysentery, asthma, renal calculus, glomerulonephritis, erysipelas, sickle cell anemia and Hodgkin's disease, and a febrile group consisting of children with acute infection of the upper respiratory tract, rheumatic fever, pneumonia and tuberculosis. The results are presented in table 11.

Dark Adaptation in Infection.—Dark adaptation, or ability to see in dim light, is dependent on the regeneration of rhodopsin, visual purple, after the eyes have been exposed to a bright light. The synthesis of rhodopsin, a photosensitive pigment located in the outer segment of the rods, is related to vitamin A. In the

52. Josephs, H. W.: Vitamin A and Total Lipid of the Serum in Pneumonia, Am. J. Dis. Child. **65**:712 (May) 1943.

presence of a deficiency of vitamin A, regeneration occurs slowly, with resulting poor dark adaptation and night blindness.



A method has been evolved by the use of the biophotometer to measure dark adaptation. Jeans, Blanchard and Satterthwaite [53] in 1941 in a review of the subject pointed out that their results were consistent and valid and were apparently a reliable index of the vitamin A status of the patient.

Poor dark adaptation is among the first symptoms of vitamin A deficiency and precedes by a long time the development of cornification of the normal epithelium of the conjunctiva, respiratory tract and urinary tract.

Getz, Hildebrand and Finn [54] in a study of dark adaptation of patients with tuberculosis as compared with that of normal persons noted that 6.5 and 11 per cent of two control groups and 53 per cent of the group with tuberculosis had evidence of abnormal dark adaptation. In the normal groups, dietary inadequacy could not possibly explain more than one half of the abnormalities. It is interesting to find that in this group 53.3 per cent had postnasal discharge and 60 per cent had had more than four colds per year. That infection possibly played the greatest role in production of the abnormal dark adaptation in the control subjects became more apparent when the authors considered the 53 per cent of the patients with tuberculosis who showed a deficiency during the test. These patients were ambulatory and afebrile, and not only had all of them had diets which were adequate in vitamin A but 40 per cent had been receiving supplementary concentrates of fish liver oil. Furthermore, there was a parallelism between the severity of the pulmonary tuberculosis and the degree of abnormality in dark adaptation.

Jeghers,[55] in recording the results of biophotometer tests in a group of 160 students, noted that 35 per cent had subnormal levels. Because the vitamin A intake in this group ranged between 900 and 5,500 units as compared with the intake in the normal group of 3,300 to 9,000 units, he concluded that the cause for the abnormal dark adaptation was the inadequate intake. However, he noted that although 12 per cent of the normal group had chronic localized mild infections, 34 per cent of the subnormal group had chronic infections, all of which tended to be of more serious type than those in the normal group.

Jeans, Blanchard and Satterthwaite [53] in 1941 definitely attributed the loss in dark adaptation in supposedly normal persons to infection rather than to inadequate intake of vitamin A. In a study of 120 school children only 5 per cent had subnormal results in the fall, with an increase to almost 20 per cent in the winter. They attributed the deficiency to two possible causes, dietary deficiency and utilization deficiency. The latter term was considered as covering difficulty in absorption or in hepatic function or possibly in destruction of vitamin A or in diversion of supply temporarily to some other use than for dark adaptation. They

53. Jeans, P. C.; Blanchard, E. L., and Satterthwaite, F. E.: Dark Adaptation and Vitamin A, J. Pediat. **18**:170, 1941.

54. Getz, H. R.; Hildebrand, G. B., and Finn, M.: Vitamin A Deficiency in Normal and Tuberculous Persons as Indicated by Biophotometer, J. A. M. A. **112**:1308 (April 8) 1939.

55. Jeghers, H.: The Degree and Prevalence of Vitamin A Deficiency in Adults, with a Note on Its Experimental Production in Human Beings, J. A. M. A. **109**:756 (Sept. 4) 1937.

then pointed out that in the geographic region in which the observations were made dietary deficiency alone seemed to be the cause in only a few instances. The most frequent cause was utilization deficiency resulting from illness, particularly an acute infection. Even a minor illness in a child who had had a moderate intake of vitamin A seemed capable of decreasing dark adaptation. Also, the seasonal increase in winter seemed related to increase in infections during the winter months rather than to any seasonal variation in diet.

Thus it would appear that at least in the United States, where vitamin A deficiency is comparatively rare, dietary inadequacy is usually not in itself the cause for deficiency symptoms, such as abnormal dark adaptation, and that the symptoms are more apt to be associated with conditions which impair absorption or utilization of vitamin A.

Summary: Vitamin A in Infection.—One may conclude that acute or chronic infection affects strikingly the absorption and utilization of vitamin A in the body and that the effect may be brought about in one of five ways: (1) by decrease in appetite and thereby diminution of intake; (2) by interference with normal absorption; (3) by increased utilization, which in part may be due to fever and increased metabolism; (4) by interference with utilization either of provitamin A or of the stored vitamin A, and (5) by abnormal excretion. However, the net effect on the vitamin A status is in most disease processes not sufficient to produce any serious deficiency, and if the infection or underlying cause for lack of absorption and utilization is removed there is probably no need for increased intake of vitamin A. This has been pointed out by Clausen [14] and others who have shown that the administration of vitamin A has no effect on the course of an infection. The only exception would be infection superimposed on a severe vitamin A deficiency state.

The vitamin A status within the body also may be affected by cirrhosis of the liver, valvular lesions of the heart, thyroid disorders, malignant tumors and allergy.

CIRRHOSIS OF THE LIVER

When one considers the important role the liver plays in the metabolism of vitamin A, its absorption, storage, conversion of provitamin A and possibly the changing of vitamin A from the ester to free form, one might expect that hepatic damage would have a pronounced effect on the vitamin A status of the body. Furthermore, in patients with cirrhosis of the liver there is usually the added factor of alcoholism, the effect of which has previously been noted. Ralli, Baumann and Roberts [56] and Haig and Patek [57] have demonstrated in patients with cirrhosis of the liver a marked decrease in the vitamin A content of the liver as compared with that of normal persons and a decrease in the blood level. The latter workers have further demonstrated that the blood level seems to be a crude index of the severity of the disease. They found 65 international units per hundred cubic centimeters in patients with decompensated cirrhosis, 122 units in patients with compensated cirrhosis and 198 units in normal subjects. As regards dark adaptation, Haig and Patek noted that it is apt to be abnormal and of a "delayed" type in patients with Laennec's cirrhosis but that it is not always associated with a low blood level of vitamin A. As evidence of the mechanism responsible for the

56. Ralli, E. T.; Baumann, E., and Roberts, L. C.: The Plasma Levels of Vitamin A After Ingestion of Standard Doses: Study in Normal Subjects and Patients with Cirrhosis of the Liver, J. Clin. Investigation **20**:709, 1941.

57. Haig, C., and Patek, A. J., Jr.: Vitamin A Deficiency in Laennec's Cirrhosis: The Relative Significance of the Plasma Vitamin A and the Carotenoid Level and the Dark Adaptation Time, J. Clin. Investigation **21**:309, 1942.

deficiency, the low storage of the vitamin in the liver has been noted. Ralli, Baumann and Roberts have demonstrated a decrease in absorption after a test dose. Haig and Patek have noted that the mean vitamin A–carotene ratio of the plasma of patients with decompensated cirrhosis was significantly lower than that of patients with compensated cirrhosis or no disease at all, which suggested that conversion of carotene into vitamin A is impaired.

Therefore, it would seem that in cirrhosis of the liver deficiency of vitamin A may occur as a result of (1) decreased absorption, (2) decreased storage and (3) inability of the liver to convert provitamin A.

VALVULAR LESIONS OF THE HEART

It has been previously noted that lesions of the heart even in the absence of infection, such as congenital heart disease, may play a role in the production of malnutrition. That there also may be a disturbance in vitamin A metabolism was found by Ellison and Moore [43] and Moore,[45] who demonstrated extremely low amounts of vitamin A in the liver of patients who had died of valvular heart

TABLE 12.—*Vitamin A Absorption in Patients with Valvular Disease of the Heart*

Patient	Age, Yr.	Diagnosis	Comment	Vitamin A Fasting Blood Level, Micrograms per 100 Cc.	Level Four Hours After Ingestion of Test Dose, Micrograms per 100 Cc.
F. H.	7/12	Congenital heart disease; (?) patent auricular septal defect	Acyanotic	16.2	38.4
S. A.	6	Congenital heart disease; tetralogy of Fallot	Marked cyanosis	83.0	83.5
J. T.	10	Rheumatic heart disease; mitral insufficienty and mitral stenosis	No activity; no failure	23.0	195.5
J. P.	8	Rheumatic heart disease; mitral insufficiency and mitral stenosis	No activity; no failure	19.0	184.5
L. W.	13	Rheumatic heart disease; mitral insufficiency, mitral stenosis and aortic insufficiency	No activity; decompensation	19.9	35.8

disease. In our observations in 2 cases of congenital heart disease it was noted that absorption was decreased. In rheumatic heart disease with which there was no active infection and no cardiac failure there seemed to be no impairment. However, in an instance of severe mitral stenosis associated with decompensation absorption proved to be abnormal (table 12).

It would seem that the congestion of the liver and of the mucous membrane of the intestinal tract might be responsible for the impairment in absorption in the case of cardiac failure and that perhaps the anoxia of the same organs was the factor in cases of congenital heart disease.

MALIGNANT NEOPLASTIC DISEASE

In a metabolic study of patients with malignant neoplastic disease, Abels and associates [58] have reported that the plasma vitamin A level is depressed. The vitamin A was low both in patients with gastrointestinal cancer and in patients with malignant growths in other parts of the body. That the lowering of vitamin A in the blood was not purely the result of improper absorption was evident by

58. Abels, J. C.; Gorham, A. T.; Pack, G. T., and Rhoads, C. P.: Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract: I. Plasma Vitamin A Levels in Patients with Malignant Neoplastic Disease, Particularly of the Gastrointestinal Tract, J. Clin. Investigation **20**:749, 1941.

the inability to raise the level of vitamin A by parenteral injection. The level, however, could be raised by administration of yeast, lipocaic or choline chloride. The authors expressed the opinion that this rise might be indicative of increased mobilization rather than of improvement in the metabolism of vitamin A and that the greatest factor of interference with vitamin A was a hepatic dysfunction which was not on a basis of metastasis. It was interesting to note that in these patients the thiamine concentration of the leukocytes and the urinary excretion of riboflavin were within normal limits.

DISORDERS OF THE THYROID

Hyperthyroidism, associated as it is with an increase in rate of metabolism, is accompanied by a fall in the blood level of vitamin A. This has been demonstrated clinically in human beings [11a] and after the administration of thyroxin experimentally.[59] That there possibly exists another factor which is responsible for the decrease in vitamin A is suggested by evidence indicating an antagonism between thyroxin and vitamin A. Eufinger and Gottlieb [60] showed that the metamorphosis of the tadpole as influenced by thyroxin is delayed by the administration of vitamin A. Others have shown that in rats the effects of thyroxin are mitigated by the use of carotene or vitamin A.[61]

In hypothyroidism there is also a diminution in blood level of vitamin A. But the mechanism seems different. May and McCreary [19] have shown that in cretinism there is a decrease in intestinal absorption of vitamin A. However, the greatest factor responsible for the deficiency appears to be the inability of the liver in hypothyroidism to convert carotene to vitamin A.[62] Clausen [11a] has noted, as further evidence of this deficiency, that hypothyroidism in human beings is characterized by high blood carotene and low blood vitamin A.

In both these disorders the decrease in vitamin A is usually not sufficient to produce deficiency symptoms.

ALLERGY

Reactions of allergic character, just as infections, seem to lessen the ability of the intestinal mucosa to absorb vitamin A. Here again, the defective absorption is present despite the fact that there may be no gastrointestinal symptoms. In most instances the decrease in absorption usually persists only as long as the allergy is active. However, that allergy may produce a greater effect is indicated when one considers its possible role as an etiologic factor in the celiac syndrome. This has been discussed in a previous paper,[30] and here we may limit ourselves to the evidence of impaired vitamin A absorption during acute allergic manifestations (table 13).

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59. (*a*) Abelin, I.: Ueber die Beziehungen zwischen Carotin und Thyroxin, Ztschr. f. physiol. Chem. **217**:109, 1933. (*b*) Greaves, J. D., and Schmidt, C. L. A.: Studies on Vitamin A Requirements of Rat, Am. J. Physiol. **116**:456, 1936. (*c*) Patek, A. J., Jr., and Haig, C.: Effect of Administration of Thyroid Extract and of α-Dinitrophenol upon Dark Adaptation, Proc. Soc. Exper. Biol. & Med. **46**:180, 1941.

60. Eufinger, H., and Gottlieb, J.: Wirkungskoeffizienten des Thyroxineffektes im biologischen Versuch, Klin. Wchnschr. **12**:1397, 1933.

61. (*a*) von Euler, H., and Klussmann, E.: Carotin und Thyroxin, Ztschr. f. physiol. Chem. **213**:21, 1932. (*b*) Sheets, R. F., Jr., and Struck, H. C.: Vitamin A and the Thyroid, Science **96**:408, 1942.

62. (*a*) Fasold, H., and Heidemann, E. R.: Ueber die Gelbfärbung der Milch thyreopriver Ziegen, Ztschr. f. d. ges. exper. Med. **92**:63, 1933. (*b*) Wendt, H.: Ueber Veränderungen im Karotin-Vitamin-A-Haushalt beim Myxödem und bei Kretins, München. med. Wchnschr. **82**:1679, 1935.

It would seem from the data in table 13 that allergy, whether it is excited by food factors or by inhalants and with or without associated gastrointestinal symptoms, may impair the absorption of vitamin A.

CONCLUSIONS

It is to be hoped that after the world conflict is over cooperation will be so adequate that all people of all nations will be properly fed. However, even with

TABLE 13.—*Absorption of Vitamin A in Patients with Allergy*

Patient	Age, Yr.	Diagnosis	Comment	Vitamin A Fasting Blood Level, Micrograms per 100 Cc.	Level Four Hours After Ingestion of Test Dose, Micrograms per 100 Cc.
J. V.	5/12	Atopic eczema	Active 4+ reaction to milk.....	24.9	24.1
			After period on amigen.....	17.6	196.0
B. P.	11/12	Atopic eczema	Erythematous eruption and secondary infection	39.4	48.3
M. B.	1 4/12	Atopic eczema	Lesion limited to cheeks.....	30.2	98.6
D. F.	8/12	Atopic eczema	Free interval	35.2	48.3
C. T.	3	Atopic eczema	Active	24.2	44.0
S. G.	3	Atopic eczema	Free interval	19.0	186.0
J. K.	11	Atopic eczema; asthma	Asymptomatic	18.7	97.0
J. B.	8½	Chronic eczematoid dermatitis	29% eosinophils; severe reactions to foods	15.8	106.0
E. P.	9	Chronic eczematoid dermatitis	Cutaneous reactions negative except 2+ to milk	37.3	118.0
B. F.	12	Hay fever	During symptoms	15.3	21.6
			Four days later, after amelioration of symptoms	17.8	65.6
M. T.	11	Hay fever	During season	4.8	33.4
			Free interval	28.3	289.0
T. W.	4	Asthma	Wheezing; 30% eosinophils; reacted chiefly to inhalants	20.5	58.8
B. W.	7	Asthma; allergic rhinitis	Asthmatic episode; inhalants chief reactors	25.3	23.2
R. S.	9	Asthma; allergic rhinitis	Asthmatic episode 2 days before test	19.6	37.9
J. D.	3	Asthma	Asthmatic episode 2 days before test; no reactions to food; to dust 3+	27.4	99.3
J. K.	10	Asthma	Active	20.0	57.7
J. D.	5	Asthma	Asthmatic episode 1 day before test	17.1	88.0
F. S.	11	Asthma	Asymptomatic	21.0	60.8
W. K.	10	Asthma	Asymptomatic; chief reactors, grasses, dust and alternaria	23.2	92.2
M. M.	13	Asthma; allergic rhinitis	Asymptomatic; 4+ reaction to grasses, dust and navy beans	47.2	265.8
B. R.	9	Asthma; allergic rhinitis	Asymptomatic; reactions chiefly to inhalants; 2+ to tomatoes and oats	36.5	125.0

food supplies ample and available, it may be expected that the problems of malnutrition will persist. This becomes evident as one considers the causes of failure to gain as observed in infants and children at the present time in the United States. In only a small percentage is improper feeding the responsible factor. Usually malnutrition has been found to be the result of organic disturbance within the patient. Therefore, if one expects to cope with the problems of malnutrition in the future, it seems obvious that more attention should be focused on investigations of the effects of disease on nutrition.

In this paper a review of the effects of disease processes on the status of the body as regards vitamin A is presented.

EFFECT OF ADOLESCENCE ON BASAL METABOLISM OF NORMAL CHILDREN

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AND

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Standards for the basal metabolism of children from 2 to 15 years old, inclusive, have been reported recently by Lewis, Duval and Iliff.[1] The data on which these standards were established have been used here in an attempt to resolve some of the confusion which exists in the literature with regard to the effect of adolescence and its attendant growth spurts on the basal metabolism.

REVIEW OF LITERATURE

Many workers have felt that there is a prepubertal or pubertal rise in the metabolism, but little agreement can be found in the literature with regard to the extent of such changes, if they do occur, or to the time of their appearance. It is of interest to note that as early as 1843 Andral and Gavarret[2] made special mention of the effect of the onset of puberty on the production of carbon dioxide. They concluded that the increase in exhaled carbon dioxide noted for both sexes with increasing age suddenly becomes extreme in boys at puberty but levels off in girls with the onset of the menses.

Olmstead, Barr and Du Bois[3] reported that 7 boy scouts 14 or 15 years old showed a considerable decrease in calories per hour per square meter below the values found for them two years earlier by Du Bois.[4] This rapid decrease in a period of two years combined with the fact that the values obtained when these boys were 12 or 13 years old were higher than those previously found for younger children led Du Bois to suggest a specific increase in the metabolism of boys of this age that is related to the renewed increase in growth which is characteristic of the period of prepubescence. These conclusions have been criticized by Bene-

From the Child Research Council and the Department of Biochemistry of the University of Colorado School of Medicine.

This report is taken from the dissertation submitted by Anna Marie Duval to the Faculty of the Graduate School of the University of Colorado, June 1942, in partial fulfilment of the requirements for the degree Doctor of Philosophy.

A preliminary report of this study was made at the meetings of the Colorado-Wyoming Academy of Science at Golden, Colo., in November 1941 (J. Colorado-Wyoming Acad. Sc. **3**:55 [April] 1942).

1. Lewis, R. C.; Duval, A. M., and Iliff, A.: Standards for the Basal Metabolism of Children from Two to Fifteen Years of Age, Inclusive, J. Pediat. **23**:1 (July) 1943.

2. Andral, G., and Gavarret, J.: Recherches sur la quantité d'acide carbonique exhalé par le poumon dans l'espèce humaine, Ann. de chim. et phys. **8**:129, 1843.

3. Olmstead, W. H.; Barr, D. P., and Du Bois, E. F.: Clinical Calorimetry: XXVII. Metabolism of Boys Twelve and Fourteen Years Old, Arch. Int. Med. **21**:621 (May) 1918.

4. Du Bois, E. F.: Clinical Calorimetry: XII. The Metabolism of Boys Twelve and Thirteen Years Old Compared with the Metabolism at Other Ages, Arch. Int. Med. **17**:887 (June) 1916.

dict and Talbot [5] and by Bierring [6] on the basis of the small number of cases involved and because the results of successive periods in the first series of determinations varied from each other too widely to be averaged legitimately. In 1927 Du Bois [7] admitted the validity of such criticism but reaffirmed his belief that the energy metabolism, expressed as calories per hour per square meter, is higher before puberty than at adjacent ages.

Benedict and Talbot [5] failed to find any effect of prepubescence on the metabolism, since some of the results obtained on both boys and girls approaching puberty were higher and some lower than the standards extrapolated from earlier ages. Benedict and Hendry [8] found little difference between the basal metabolism of girls who had reached puberty and of those who were still prepubescent. Blunt, Tilt, McLaughlin and Gunn [9] reported that neither their average values nor their individual data showed any effect of adolescence on the basal metabolism.

Göttche [10] found an increase in the basal metabolism in the first stage of puberty in about half of the children studied. However, the amount of change did not correspond well with the clinical signs of sexual development. The results of Lax and Petényi,[11] when subjected to critical analysis, add little to the available information on the effect of puberty on basal metabolism. When total calories were plotted against age for the range studied, 11 to 16 years inclusive, the curve rose to a peak at 14 years and then dropped sharply. However, no values were available at the 15 year age level, and the only 16 year old subject was a comparatively small child who might be expected to have a lower total heat production. When calories per kilogram were plotted against age, there was a slackening in the rate of fall of the curve between 11.5 and 12.5 years of age. Because the sex of the subjects was not given, these results cannot be compared with those of other studies with regard to the age at which adolescent changes occur.

Rosenblüth [12] found that the greatest variability in the basal metabolism of the boys studied by him occurred between 14 and 16 years of age, and he felt that this was related to puberty. Bierring [6] observed some tendency for his results, expressed as calories per hour per square meter referred to age, to decrease less rapidly in the interval between 14 and 15 years. A similar tendency was noted in the interval between 42 and 50 Kg. for total calories per kilogram referred to body weight. Thus, he was the first worker to suggest the possibility of a relative increase in the metabolism at puberty in the sense that the rate of decrease becomes less marked. When Bruen [13] in 1933 subjected the results of

5. Benedict, F. G., and Talbot, F. B.: Metabolism and Growth from Birth to Puberty, Publication 302, Carnegie Institution of Washington, 1921.

6. Bierring, E.: The Standard Metabolism of Boys (Seven to Eighteen Years, Inclusive), Copenhagen, Levin & Munksgaard, 1931.

7. Du Bois, E. F.: Basal Metabolism in Health and Disease, ed. 2, Philadelphia, Lea & Febiger, 1927, p. 147.

8. Benedict, F. G., and Hendry, M. F.: The Energy Requirements of Girls from Twelve to Seventeen Years of Age, Boston M. & S. J. **184**:217 (March 3); 257 (March 10); 282 (March 17); 297 (March 24); 329 (March 31) 1921.

9. Blunt, K.; Tilt, J.; McLaughlin, L., and Gunn, K. B.: The Basal Metabolism of Girls, J. Biol. Chem. **67**:491 (Feb.) 1926.

10. Göttche, O.: Gasstoffwechseluntersuchungen im Kindesalter: Die Pubertätsreaktion, Monatschr. f. Kinderh. **32**:22, 1926.

11. Lax, H., and Petényi, G.: Der Grundumsatz im Pubertätsalter, Monatschr. f. Kinderh. **36**:385, 1927.

12. Rosenblüth, A.: Der Grundumsatz bei Kindern und Jugendlichen, Ztschr. f. Kinderh. **46**:531, 1928.

13. Bruen, C.: Variation of Basal Metabolic Rate per Unit Surface Area: II. Pubertal Acceleration, J. Nutrition **6**:383 (July) 1933.

Bierring to statistical analysis and used a nine point moving median in plotting the data, he found a retardation in the decrease in calories per hour per square meter during the thirteenth year, a distinct rise in the fourteenth year and an accelerated decline subsequently. He also demonstrated that the results of Göttche [10] and of Topper and Mulier,[14] expressed as the percentage deviation from the standard used, indicated an upward prepubescent trend and a downward trend in the period following puberty. Bruen concluded that the variation in calories per hour per square meter with age during puberty may be the resultant of a fundamental decrease with age and a superimposed acceleration.

A study of the puberty reaction by a procedure suggested by Du Bois,[7] whereby the basal metabolism of a group of children was determined every six months between the ages of 10 and 16 years, was made by Topper and Mulier.[14] They expressed their results as the percentage deviations from the Pirquet sitting height standard and found increased values for 12 to 13 year old girls and for 13 to 14 year old boys that decreased again after puberty was established. They concluded that the basal metabolism shows a prepubertal rise which is individual and cannot be predicted from the preceding metabolism.

Nylin [15] reported that for girls the standard metabolism per square meter of body surface or per kilogram of body weight, functions which ordinarily decrease with increasing age, either increased or remained constant during that part of puberty characterized by marked growth in height. He concluded that these findings are strong evidence that an increase in combustion takes place in the organism during this period. However, de Biehler [16] found no particular increase in the oxygen consumption of girls during puberty except in those who showed enlargement of the thyroid gland.

Nakagawa [17] demonstrated that for Japanese children a greater increase in total basal heat production occurs at 12 to 13 years in boys and at 11 to 12 years in girls than at adjacent ages. No consistent chronologic relationship between the period of increased heat production and the time of maximum increase in height or weight could be found.

The standards of Boothby, Berkson and Dunn [18] for basal metabolism show a much less marked yearly rate of decrease in calories per hour per square meter from 11 to 16 years of age for boys and from 8 to 11 years of age for girls than during adjacent ages.

Webster, Harrington and Wright [19] found a significant decrease in calories per hour per square meter between the ages of 11 and 12 years in both boys and girls, but no significant change in the mean metabolism at any later age. Thus, they concluded that there is no significant increase in calories per hour per square meter in the period between the ages of 11 and 14 years. However, a study of

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14. Topper, A., and Mulier, H.: Basal Metabolism of Normal Children: The Puberty Reaction, Am. J. Dis. Child. **43**:327 (Feb.) 1932.

15. Nylin, G.: The Physiology of the Circulation During Puberty, Acta med. Scandinav. (supp.) **69**:1, 1935.

16. de Biehler, M.: Metabolisme basal et fonction métabolique de la glande thyroïde à l'époque de la puberté chez les filles, Arch. de méd. d. enf. **40**:274 (May) 1937.

17. Nakagawa, I.: Growth and Basal Metabolism: VI. Changes in the Basal Metabolism of Children During Puberty, Am. J. Dis. Child. **53**:991 (April) 1937.

18. Boothby, W. M.; Berkson, J., and Dunn, H. L.: Studies of the Energy of Metabolism of Normal Individuals: A Standard for Basal Metabolism, with a Nomogram for Clinical Application, Am. J. Physiol. **116**:468 (July) 1936.

19. Webster, B.; Harrington, H., and Wright, L. M.: The Standard Metabolism of Adolescence, J. Pediat. **19**:347 (Sept.)) 1941.

their mean values reveals a leveling off of the metabolism between 12 and 15 years in boys and between 12 and 13 years in girls. This may well correspond to the relative increase suggested by Bierring.[6]

Comparison of the results of the aforementioned papers which purport to show a pubertal effect on the metabolism is difficult because of the discrepancies which exist in the methods of reference used. In some instances a function of the metabolism which decreases with age through the greater part of childhood, as, for example, calories per hour per square meter, has been used, and disagreement exists as to whether an absolute increase occurs at puberty or whether the increase is only relative, as manifested by a diminished rate of decrease. In other instances a function, such as total heat production, which increases with increasing age or body size has been used, and attempts have been made to determine whether the increase at puberty is greater than that at other periods. Still other workers have used the basal metabolic rate expressed as the percentage deviation of the observed from the standard value as a basis for discussion, and this would

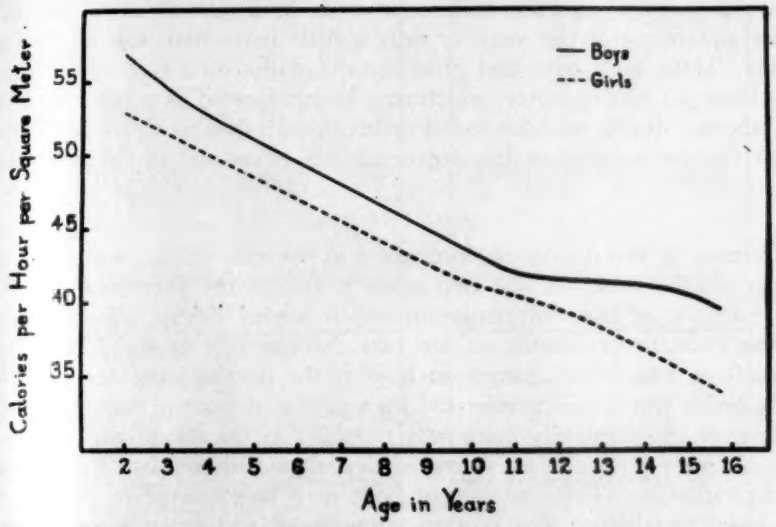

Chart 1.—General trends of the standard values for basal metabolism, expressed as calories per hour per square meter referred to age, for boys and girls.

appear to involve the assumption that pubertal effects have not been reflected in the standard values used for comparison.

In view of the widely divergent ages at which individual children begin to show adolescent changes and of the variation in the speed with which these changes progress, it is not surprising that the age at which prepubertal or pubertal changes in the metabolism are said to occur varies in the different studies. Since some of the reports have been based on observations on only a small number of children, chance selection has in all probability weighted the results unduly.

EXPERIMENTAL DATA

The experimental data from which this study is made comprise 1,007 determinations of basal metabolism on 70 boys and 718 determinations on 57 girls. The subjects are members of the group of healthy children who are being followed regularly from birth to maturity by the Child Research Council. Repeated determinations of basal metabolism have been made on each subject at intervals of from three to five months with the open circuit chamber procedure. A complete description of the apparatus and of the technic employed has been

given by Lewis, Kinsman and Iliff.[20] Their study and those of Lewis, Duval and Iliff [21] have furnished the experimental results from which standard values for basal metabolism have been computed and reported by Lewis, Duval and Iliff.[1] A study of the general trend of these standard values, particularly those for calories per hour per square meter referred to age, reveals certain interesting changes during adolescence.

Chart 1, which depicts calories per hour per square meter plotted against age, reveals a linear fall in the values for boys which amounts to approximately 1.5 calories per hour per square meter per year between the ages of 3 and 11 years. Here the decrease becomes much less marked and in the four year period from 11 to 15 years averages approximately 0.4 calory per hour per square meter per year, or a rate only a little more than one fourth as great as in the earlier years. During the next year the decrease is accelerated over that found in this period of slackening of the rate of fall. The comparable data on girls reveal a similar but less striking picture. In early childhood the general trend of the standard values for calories per hour per square meter is to decrease at a rate of approximately 1.4 calories per hour per square meter per year to the age of 10 years. From 10 to 12 years of age the decline proceeds at a rate of about 0.8 calory per hour per square meter per year, or only a little more than half as fast as in earlier years. Thus, both boys and girls show a diminished rate of decrease of calories per hour per square meter, which may be interpreted as a relative increase in basal metabolism during adolescence. Furthermore, a definite difference between boys and girls is to be noted in the degree of this effect and in the time during which it occurs.

COMMENT

The difference in the degree of diminution in the rate of decrease of calories per hour per square meter in the two sexes noted in the preceding paragraph may be a reflection of the differentiation which begins during adolescence and results in the ultimate production of the two characteristic types of body build. The end result of adolescent changes in boys is the development of a masculine type of body build, which is characterized by a preponderance of actively metabolizing muscle over comparatively inert fatty tissue. On the other hand, adolescent development in girls results in an increased deposit of subcutaneous fat and little change in musculature. Thus, adolescent boys may be expected to show a relatively high basal metabolism that is more pronounced and extends over a longer period of time than is the case for adolescent girls. That the standard values for calories per hour per square meter for the girls undergo a period of diminished rate of decrease at an earlier age than do those for the boys is compatible with the fact that in general girls begin to show adolescent changes in the secondary sex characteristics at an earlier age than boys.

The relative increase in the mean basal metabolism found during adolescence confirms the results of Bierring [6] but is not in agreement with those of Du Bois,[4] who reported an absolute increase. However, it is likely that chance of selection may account for these discrepancies, since some subjects in the present study have also shown an absolute increase in calories per hour per square meter at adolescence. Thus, it seems probable that such an absolute increase in the mean

20. Lewis, R. C.; Kinsman, G. M., and Iliff, A.: The Basal Metabolism of Normal Boys and Girls from Two to Twelve Years Old, Inclusive, Am. J. Dis. Child **53**:348 (Jan.) 1937.

21. Lewis, R. C.; Duval, A. M., and Iliff, A.: Basal Metabolism of Normal Boys and Girls from Two to Twelve Years Old, Inclusive: Report of a Further Study, Am. J. Dis. Child. **65**:834 (June) 1943; Basal Metabolism of Normal Children from Thirteen to Fifteen Years Old, Inclusive, ibid. **65**:845 (June) 1943.

values will be found only in those instances in which too small a number of children has been studied to afford a good sampling of all degrees of variation.

In the present report the period of relatively elevated basal metabolism noted for the boys extends from 11 to 15 years of age. This range includes the periods of adolescent changes in basal metabolism found by Du Bois,[4] by Bierring,[6] by Topper and Mulier,[14] by Nakagawa [17] and by Webster, Harrington and Wright [19] but terminates a year sooner than that of Boothby, Berkson and Dunn.[18] Du Bois and Nakagawa found elevated values for 12 to 13 year old boys, while Topper and Mulier have reported high results for 13 to 14 year old boys. The period of relative increase found by Bierring for 14 to 15 year old boys falls in the latter part of the range for the present study. The results of Webster, Harrington and Wright indicate a relatively elevated basal metabolism for boys from 12 to 15 years of age. The period of relatively high values for calories per hour per square meter found for the 10 to 12 year old girls of the present study begins somewhat later than that noted, from 8 to 11 years of age, by Boothby, Berkson

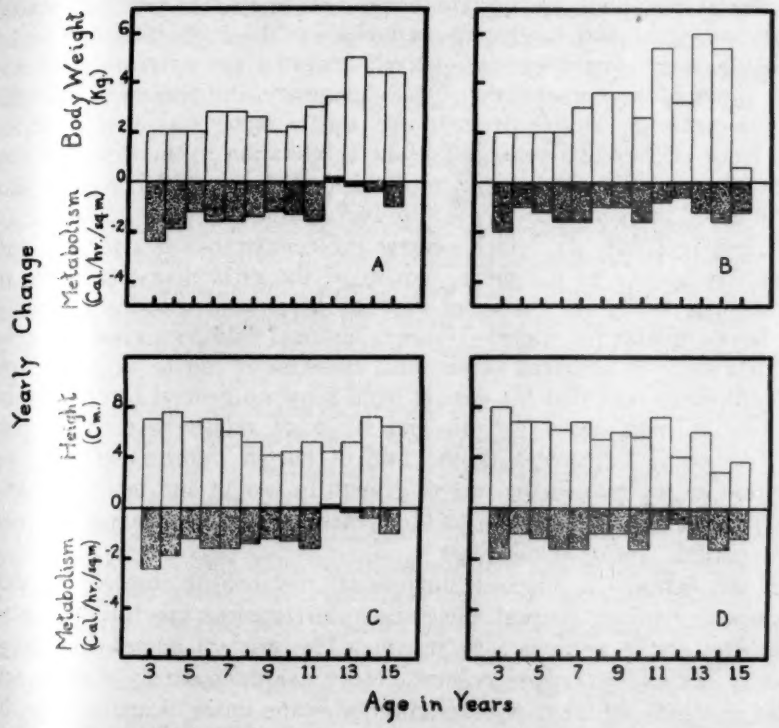

Chart 2.—Comparison of the average yearly changes in body size and in basal metabolism. Graphs *A* (for boys) and *B* (for girls) show the average gain in weight per year compared to the average yearly change in calories per hour per square meter. Graphs *C* (for boys) and *D* (for girls) show the average increase in height per year compared to the average yearly change in calories per hour per square meter.

and Dunn. Nakagawa found high values for the basal metabolism of 11 to 12 year old girls, while the results of Topper and Mulier and of Webster, Harrington and Wright are elevated for 12 to 13 year old girls.

It was suggested by Du Bois [4] in 1916 and again by Talbot [22] in 1938 that the basal metabolism of adolescent children might be comparatively higher than

22. Talbot, F. B.: Basal Metabolism Standards for Children, Am. J. Dis. Child. **55**:455 (March) 1938.

that of younger or older children because of the stimulating effect of the growth spurts characteristic of this period of life. In view of a possible relationship between the speed of growth and the level of the basal metabolism, the data herein discussed have been compared with the average yearly growth rates of the same children to determine whether the period of relatively high basal metabolism coincides with that of maximum increment in weight and height. Chart 2 presents a comparison of the average yearly changes in calories per hour per square meter with changes in weight and height, respectively, for both boys and girls. The average yearly growth rates are taken as the differences between successive mean values for weight and height reported by Lewis, Duval and Iliff [1] for each age period. Similarly, the average yearly changes in calories per hour per square meter have been computed from the mean values indicated for each age period on the scatter diagrams included in that report. Each block in chart 2 represents a period extending from six months below to six months above the indicated age.

It is obvious from graphs *A* and *C* (chart 2), in which the average yearly changes in calories per hour per square meter are compared with the average yearly growth in weight and height, respectively, for the boys, that the periods during which the basal metabolism is relatively elevated are not coincident with those of most rapid adolescent growth. On the contrary, the observed diminution in the rate of decrease of calories per hour per square meter was already evident in the period from 11.5 to 12.5 years, while the acceleration in the rate of growth did not reach its maximum for weight until the period from 12.5 to 13.5 years and for height until the period from 13.5 to 14.5 years.

Graphs *B* and *D* (chart 2), which present the comparable data for the girls, reveal greater irregularity in the mean growth of the girls than was noted for the boys. This may be due to chance of selection because of the smaller number of girls than boys available for study. Hence, additional data on a greater number of different girls must be analyzed before final conclusions can be drawn. However, it is of interest to note that the data at hand show no general correspondence between periods of most rapid growth and those of relatively elevated basal metabolism. Although a decrease in the rate of fall in calories per hour per square meter and an increase in the rate of growth in weight and height occurred simultaneously in the period from 10.5 to 11.5 years, no such correlation is evident in subsequent periods during adolescence.

How well the periods of relatively high basal metabolism observed in these children correspond to their general adolescence development may be determined by a consideration of the average ages at which the onset of adolescent changes in the secondary sex characteristics occurs. There are undoubtedly discrepancies in the manner in which different pediatricians judge the onset of adolescence, but the ages reported in the records of the pediatric staff of the Child Research Council are probably a fair estimate of the beginning of adolescent changes. These occurred at an average age of 12 years 3 months, with a range of from 10 years 9 months to 13 years 11 months, for the boys and at an average age of 10 years 7 months, with a range of from 8 years 3 months to 13 years 3 months, for the girls. These average ages fall in the earlier part of the periods of a diminished rate of decrease in calories per hour per square meter of body surface. Thus, in general the basal metabolism appears to be relatively elevated at that period of life when adolescent changes in the secondary sex characteristics are beginning to take place.

An interesting comparison may be made between the results of the determinations of basal metabolism of adolescent children herein reported and the observations

of Nathanson, Towne and Aub [23] on the normal excretion of the sex hormones in childhood. They found the excretion of androgens in boys and of estrogens in girls to be fairly constant during early childhood, to increase gradually from about 8 to 11 years of age and then to increase rapidly to adult values. No cyclic excretion of androgens was noted in boys, but cycles appeared in the excretion of estrogen by the girls about one and one-half years before the menarche. These results led Nathanson, Towne and Aub to conclude that the menarche in girls and sexual maturity in boys are the culmination of an endocrine development which is gradual until approximately one and one-half years preceding maturity, when an additional mechanism appears which leads to a more rapid differentiation of sex characteristics. This period of increased gonadal activity corresponds well chronologically to the period of relatively high metabolism noted in the present study.

The complexity of the physiologic changes which take place at adolescence renders it difficult, if not impossible, to establish cause and effect relationships between these changes. Certainly, the relatively increased basal metabolism seen in children in the early stages of adolescence cannot be ascribed to any single factor. A longitudinal study, such as that being carried out by the Child Research Council on a large group of healthy children, may lead in time to an understanding of the chronologic relationship of these adolescent changes to one another.

SUMMARY

A review of the literature on the basal metabolism of children during adolescence fails to show agreement that an increased metabolism occurs at this period of life. The results of 1,725 determinations of basal metabolism on 70 boys and 57 girls from 2 to 15 years old, inclusive, that have been made in this laboratory during the past ten years to establish standards for children of these ages, have been used here in an attempt to resolve some of the confusion which exists in the literature in regard to this question.

No absolute increase in the mean basal metabolism expressed as calories per hour per square meter in relation to age is noted at puberty. However, the rate of decrease of the standard values for boys from 11 to 15 years old is only a little more than one fourth as great as that in the earlier years, and for girls from 10 to 12 years old the decline proceeds at a rate a little more than half as great as for younger girls. This diminution in the rate of fall of calories per hour per square meter with age may be interpreted as a relatively increased metabolism during adolescence.

No fixed relationship is to be found between the time of occurrence of maximum adolescent growth either in weight or in height and the relatively high basal metabolism which occurs during the early stages of puberty.

4200 East Ninth Avenue.

23. Nathanson, I. T.; Towne, L. E., and Aub, J. C.: Normal Excretion of Sex Hormones in Childhood, Endocrinology **28**:851 (June) 1941.

Case Reports

VON GIERKE'S DISEASE (GLYCOGEN DISEASE OF HEPATOMEGALIC TYPE)

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In 1929 von Gierke [1] reported his first case and described the glycogen disease bearing his name. Snapper and van Creveld [2] had reported an extensive clinical study of a case the year before, and abnormal accumulations of glycogen had been recognized post mortem in livers previously. "Glycogen disease," as the term was used by van Creveld [3] in his excellent review of the syndrome in 1939 and by others, has come to include, as pointed out by Mason and Andersen [4] recently, a variety of clinical and pathologic pictures. In general there is a disorder of carbohydrate metabolism beginning at a very early age and characterized by storage of glycogen in abnormally large quantities in various organs, especially the liver, the kidneys and the heart. The causes may not necessarily be similar. Mason and Andersen [4] made a tentative classification of the forms of the disease as described in the reported cases, distributing them into numerous groups and subgroups but assigning all to two main divisions, as did van Creveld [3]: (1) forms in which the main deposit of glycogen is in the liver but may be present in other organs, especially the kidneys (glycogen disease of the hepatomegalic type); (2) forms in which the main deposit is in the muscles, especially the heart muscle. In the case reported here and in the first case described by von Gierke, in 1929, the condition falls into the first, and major, group of these two divisions.

No cause for any of these forms of glycogenesis has been established, but several lines of approach have been suggested. Van Creveld [3] wrote that the disorder is perhaps a continuation of a fetal condition. There are large amounts of apparently normal glycogen stored in the fetal liver, and this glycogen is resistant to mobilization into the blood stream as dextrose by action of epinephrine, as is so in this disease. Schönheimer [5] and others [6] found no abnormalities in the glycogen obtained from the tissue of patients with the disease which they studied; Kimmelstiel [7] expressed the opposite view. Mason and Andersen [4] stated the belief that the defect in the hepatomegalic type is in the enzyme system responsible for conversion of dextrose to glycogen and the glycogen to dextrose in the liver. In the case which they studied they found, as has been noted before, flat curves for

From the Pediatrics Service and the Laboratory of Rhode Island Hospital, Providence, R. I.

1. von Gierke, E.: Hepato-Nephromegalia glykogenica (Glykogenspeicherkrankheit der Leber und der Nieren), Beitr. z. path. Anat. u. z. allg. Path. **82**:497, 1929.
2. Snapper, I., and van Creveld, S.: Un cas d'hypoglycémie avec acétonémia chez un enfant, Bull. et mém. Soc. méd. d. hôp. de Paris **52**:1315, 1928.
3. van Creveld, S.: Glycogen Disease, Medicine **18**:1, 1939.
4. Mason, H. H., and Andersen, D. H.: Glycogen Disease, Am. J. Dis. Child. **61**:795 (April) 1941.
5. Schönheimer, R.: Ueber eine eigenartige Störung des Kohlehydratstoffwechsels, Ztschr. f. physiol. Chem. **182**:148, 1929.
6. Cited by Mason and Andersen.[4]
7. Kimmelstiel, P.: Ueber Glykogenose, Beitr. z. path. Anat. u. z. allg. Path. **91**:1, 1933.

levulose and galactose tolerance and a prolonged curve for dextrose tolerance. Mashed liver tissue did not act on glycogen to produce dextrose, as tissue from the control livers did. They explained this fact on the basis that this liver probably made glycogen from levulose, galactose and perhaps other precursors of glycogen but was deficient in its ability to make glycogen from dextrose and that it was unable in any event to change glycogen back to dextrose.

REPORT OF A CASE

A 14 month old boy was admitted to the Rhode Island Hospital for study because of failure to gain weight and because of an abnormally large abdomen.

Fig. 1.—Photograph of the patient about ten days after his admission to the hospital. The approximate size of the liver is outlined. Note the large abdomen, healthy facies and emaciated limbs.

History.—The child was delivered after labor induced at eight months because of pyonephrosis of the mother. He was never breast fed. The diet was good, with supplementary orange juice and cod liver oil added appropriately. At 5 months of age he was treated for diarrhea at the outpatient department of the Rhode Island Hospital by use of a formula which eliminated cream and which was boiled for five minutes. At 13 months he had "chickenpox"; a papular rash had persisted to the time of his admission. The mother thought that the abdomen of the child had been disproportionately large since birth. His appetite was good, and there was no vomiting. There were three to four rather bulky pale brown stools daily.

No family history of similar disease was obtained.

Physical Examination.—On admission, the patient was a small, poorly developed 14 month old boy weighing 16 pounds (7,260 Gm.). His face was full and had good color; his limbs were thin, and the muscles were flabby (fig. 1). There was little subcutaneous tissue other

than on the face. The abdomen was large and had a circumference of 20 inches (51 cm.) (normal 17 to 18 inches [43 to 46 cm.]) to his height of 27 inches (69 cm.); the superficial veins were moderately prominent, especially over the upper half. The edge of the liver was found to be down to the right iliac crest, below the umbilicus at the midline by 2 to 3 inches (5 to 8 cm.), and it was difficult to differentiate the left lobe from the spleen.

Laboratory Data.—Examination of the blood showed a hemoglobin content of 11 Gm. per hundred cubic centimeters (76 per cent of the Hellige standard, of 14.5 Gm.) and a red cell count of 3,600,000 per cubic millimeter. There were 12,500 white cells per cubic millimeter, of which 14 per cent were polymorphonuclear leukocytes, 84 per cent lymphocytes and 2 per cent monocytes.

The Wassermann reaction was negative. Tests with old tuberculin in dilutions of 1:10,000 and 1:1,000 elicited negative reactions.

Stools were examined on two occasions. They showed no free fat microscopically and gave negative reactions to tests with iodine for starch.

Numerous samples of morning urine were examined. Tests for protein always gave negative reactions, and the sediments revealed nothing of significance. Tests for sugar gave negative reactions until the thirtieth day in the hospital, when a 1 plus reduction was found.

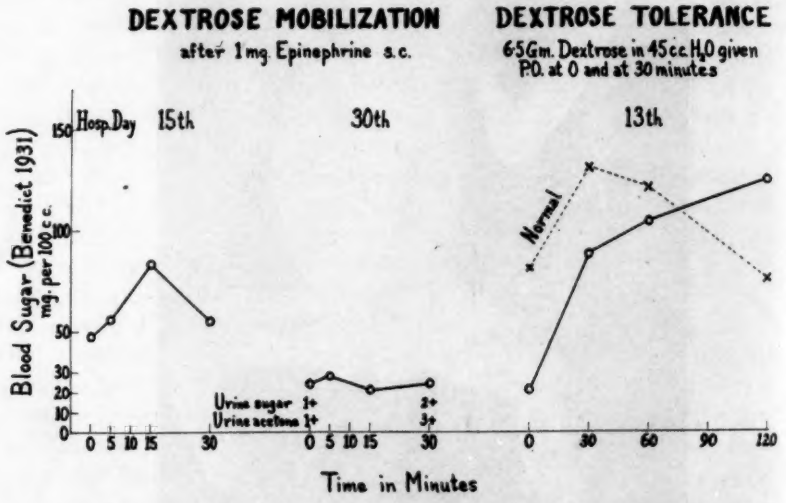

Fig. 2.—Results of tests for mobilization of and tolerance for dextrose.

A 1 plus reduction was present the next day, but not on the thirty-third day. By yeast fermentation the second positive reduction was shown to be due to dextrose and not to a nonsugar-reducing substance.

Tests for acetone in the urine gave negative reactions on the fifteenth and sixteenth hospital days, but gave positive reactions (1 plus) on the twenty-sixth, twenty-eighth, thirtieth and thirty-first hospital days. Simultaneous tests for acetoacetic acid were all negative.

Roentgenograms showed both sides of the diaphragm to be high in position; the shadow of the liver was greatly enlarged, but the lungs and skull were not remarkable.

The urea nitrogen content of the blood was 14 mg. per hundred cubic centimeters, and the protein content of the plasma was 6.0 Gm. The icteric index was estimated (on postprandial lipemic serum) as between 20 and 30. The van den Bergh reaction (direct) was immediate. The cholesterol content of the serum was 712 and 664 mg. per hundred cubic centimeters on two occasions. The cholesterol content of the serum of the father and of the mother were 100 and 186 mg. respectively.

Values for fasting blood sugar were as follows (expressed in milligrams per hundred cubic centimeters): on the tenth hospital day, 30; on the thirteenth day, 20; on the fifteenth day, 47; on the sixteenth day, 20, and on the thirtieth day, 23.

The inorganic phosphorus content of the plasma was 4.0 mg. per hundred cubic centimeters, determined on the first blood which had a fasting sugar level of 20 mg.

On the thirteenth day in the hospital a dextrose tolerance test was done. The fasting blood sugar level was 20 mg. Six and five-tenths grams of dextrose dissolved in 45 cc. of water was given by mouth, and one-half hour later the blood sugar level was 88 mg. A second 6.5 Gm. of dextrose in 45 cc. of water was given, and one-half hour later the blood sugar level was 103 mg. One hour later, two hours after the initial specimen of blood was taken, the sugar level was 123 mg. The urine contained no sugar, either before or after the ingestion of dextrose.

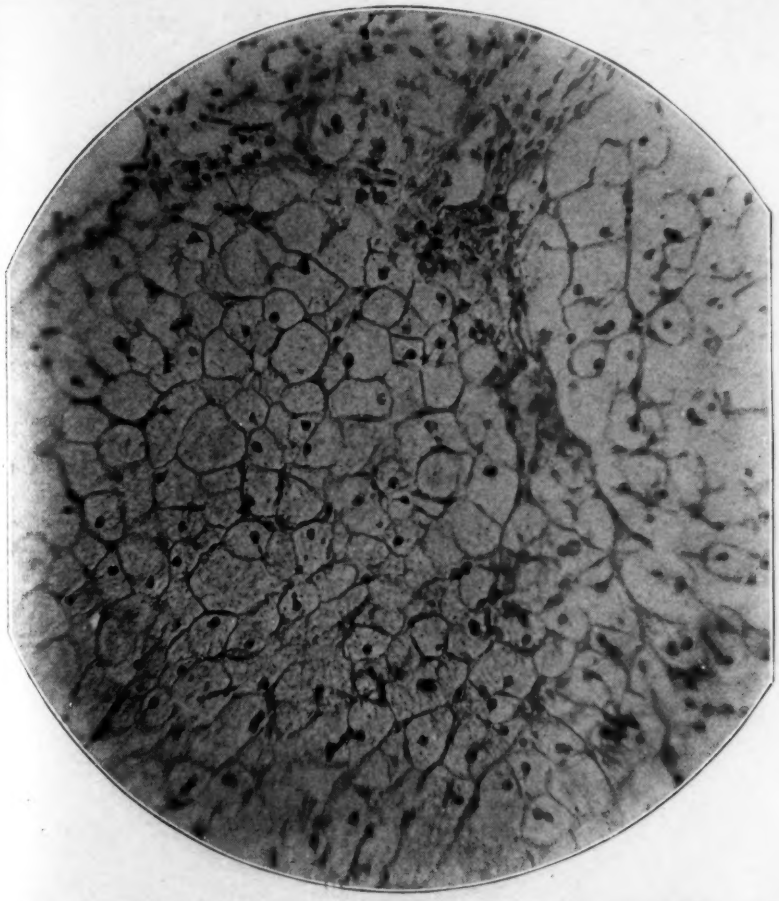

Fig. 3.—Section of liver obtained post mortem stained with hematoxylin and eosin. Note the large polygonal hepatic cells with faintly staining cytoplasm.

On the fifteenth day in the hospital 1 mg. of epinephrine hydrochloride was injected subcutaneously to determine the blood sugar response. The blood sugar increased 37 mg. above the initial level at the fifteen minute period. The urine was not tested for acetone.

Injection of epinephrine was repeated on the thirtieth hospital day. With the same dosage as previously used, the blood sugar level was only 5 mg. above the initial blood sugar level. This is probably twice the experimental error of the micromethod used. The reaction of the urine for sugar was 1 plus before the injection of epinephrine and 2 plus thirty minutes after the injection. The urinary reaction for acetone was 1 plus before and 3 plus after the injection, with a negative reaction for acetoacetic acid.

The results of the tests for mobilization of dextrose and for tolerance for dextrose are presented graphically in figure 2.

Course.—In the hospital the child was rather irritable and restless, with a low grade fever at times. On some days he ate well and on others poorly; he vomited occasionally. Removal of a specimen of liver for biopsy with local anesthesia was withstood well. Acetone was not found in the urine until one week before his discharge from a thirty-three day stay, but thereafter it was constantly present in the morning specimen. During this week several Benedict tests for sugar in the urine gave a 1 plus reaction. One of these was made on a morning specimen when the fasting blood sugar level was 23 mg. per hundred cubic centimeters.

Fig. 4.—Section of liver obtained post mortem stained with Best's carmine stain. Almost all of the gray areas appear bright red on the slide, indicating the presence of large amounts of glycogen.

Of the two dextrose mobilization tests after injection of epinephrine, done under fasting conditions, the first, on the fifteenth hospital day, produced results perhaps within low normal limits. In the second test, on the thirtieth hospital day, the epinephrine produced virtually no mobilization but did increase the content of both sugar and acetone in the urine. At this time there was evidence of an apparently subsiding mild infection of the upper respiratory tract.

With a high carbohydrate–low fat diet and intramuscular injections of liver extract and vitamin B complex and added vitamins by mouth, the child weighed 1 pound (0.5 Kg.) less on discharge than on admission.

Five days after discharge he was readmitted to the hospital, because of anorexia, cough and fever, was found to have bronchopneumonia and died in three days. Autopsy was performed eight hours after death.

Necropsy.—Gross Examination: The general description of the body was as already given. The liver was very large and weighed 1,025 Gm., contrasted with the normal weight of 300 Gm. for this age. It had a slightly yellow, waxy, translucent appearance, with the edges slightly rounded. On section it was firmer than normal and with a yellowish cast especially about the central veins. The heart weighed 32 Gm. (normal for this age is 45 Gm.) and was pale and shiny but not otherwise remarkable. The kidneys weighed 30 and 26 Gm., approximately

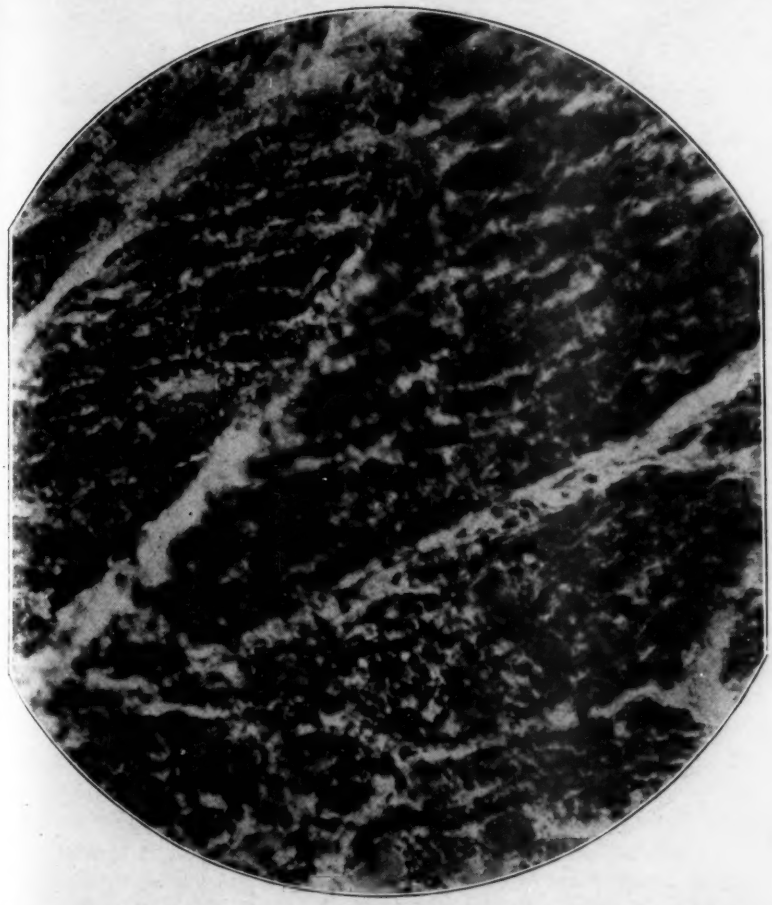

Fig. 5.—Section of cardiac muscle stained with Best's carmine stain, showing pronounced diffuse red staining (in the original slide), indicating much glycogen. These granules show best at the periphery.

normal weight. The voluntary muscle was pale. Other organs were not remarkable except for bronchopneumonia in the left lung.

Microscopic Examination.—Preliminary stains on the biopsy specimen of liver confirmed the diagnosis made clinically. The final report was not completed until the autopsy report was finished. The biopsy specimen of liver and the specimens obtained at autopsy were similar. The polygonal cells of the liver when stained with hematoxylin and eosin had a thin peripheral line and scattered delicate granules of pink-staining cytoplasm arranged about rounded clear areas. The cell nuclei were small, pyknotic and central (fig. 3). With Best's carmine stain for glycogen the hepatic cells were almost filled with varying-sized bright red-staining droplets, the largest the size of the nuclei (fig. 4).

Sections of the heart with the Best's carmine stain showed the interior of the muscle cells to be loaded with bright red-stained droplets (fig. 5). Sections of voluntary muscle stained with the same stain showed some elongated red droplets tending to be concentrated about the fibers beneath the sarcolemma, a few being scattered between the fibrils (fig. 6).

Sections of the kidneys, spleen, pancreas, thymus and lungs were stained for glycogen. Glycogen in small amounts was to be seen only in the lining cells of the renal collecting tubules.

Chemical Studies.—Analysis of sections [8] from organs was begun about nine hours after death. The results obtained are given in the table.

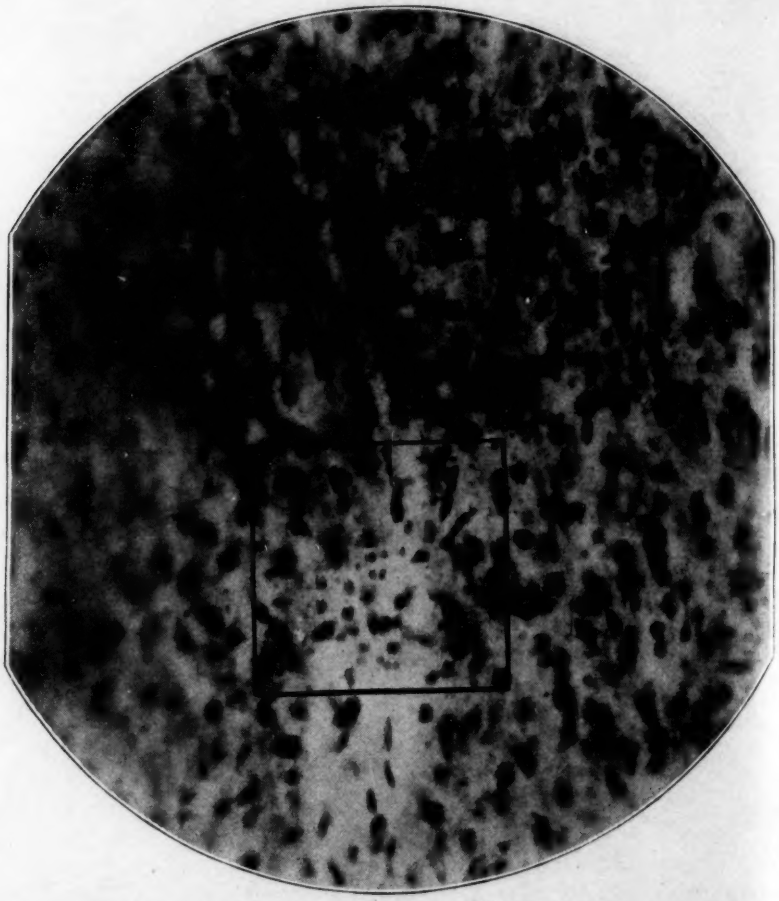

Fig. 6.—Section of voluntary muscle stained with Best's carmine stain, showing diffuse granular staining throughout. The granular staining shows best in the marked area.

8. For the determination of glycogen a weighed portion of tissue was ground with sand and extracted several times with small portions of boiling water. The combined extracts for each specimen were made acid to litmus with acetic acid, heated to boiling and filtered. After the filtered extract was cooled in the refrigerator, 4 volumes of 95 per cent ethyl alcohol was added and precipitation allowed to proceed overnight. Next morning the precipitate was filtered off, dissolved in hot water and again precipitated. After it was washed with 95 per cent alcohol the precipitate was dried at 105 C. to constant weight.

Separate specimens of tissue were weighed and dried to constant weight at 105 C. for determination of water content. They were extracted five times with ether for removal of fat, which was weighed after evaporation of the ether. The residues were ashed over a burner and reheated to constant weight, for determination of the amount of ash.

The glycogen content of the liver was found to be higher than would be expected after normal storage of carbohydrate. In the usual liver, however, the glycogen is quickly broken down post mortem, so that little or none of it is to be found after several hours. A sample of this liver was kept for twenty-one days at 4 C. It was then found to have 15 Gm. of glycogen per hundred grams of tissue, so that little or no glycogenolysis had taken place during this time. After glycogen from this liver was incubated for three days with ground liver from another subject, no glycogen could be found. The glycogen isolated from the liver was found to be identical with that from another liver in melting point (238 to 240 C.), color, reaction with iodine, digestion to dextrose by saliva and hydrolysis to dextrose with hydrochloric acid.

The heart showed more than the usual content of glycogen, 2.5 per cent of wet tissue. The kidney had normal amounts of the determined constituents.

Analyses of Organs

Organ	Percentage of Wet Weight			
	Glycogen	Fat	Ash	Water
Liver	14.0	3.6	0.8	70.6
Heart	2.5	0.4	1.1	80.0
Kidney	0.1	1.1	1.0	78.5
	Normal Values (from van Creveld [2])			
Liver	0.10	3.6		
Heart	0.07	0.1		
Kidney	0.06	0.4		

COMMENT

In this case are presented rather typical features of glycogen storage disease of the hepatomegalic type. The infant had the typical physical appearance, hepatomegaly probably dating back for some time, a low fasting level of blood sugar, ketosis and a prolonged dextrose tolerance curve. There was virtually no mobilization of dextrose into the blood stream after epinephrine was administered on the second occasion. The cholesterol level, which is variable in the reported cases, was very high. The pathologic state of the liver was typical, with the yellow, waxy appearance, the massive enlargement and the great intracellular deposits of glycogen. There was no evidence of cirrhosis. There was postmortem stability of glycogen in the liver and rapid breakdown of this glycogen in a minced preparation including normal liver. Insulin was not given to this patient, but typically patients with this disease are sensitive to its action.

No studies were done with levulose, galactose or sugars other than dextrose. Of the 34 cases of the disease that Mason and Andersen were able to collect from all the literature, urinary sugar, found at times here, was present in only 2 of the 23 cases in which tests for sugar in the urine were reported. Their hypothesis, previously mentioned, could explain the abnormalities related to carbohydrate metabolism encountered in this case. The ketosis occurs presumably because of relatively excessive fat and protein metabolism by the liver. The glycosuria is not explained, but it would seem that there was a low renal threshold; possibly the glycogen seen in small amounts in the epithelium of the renal collecting tubules can be correlated. The marked hypercholesteremia is not explained, though not unusual in the reported cases. Fat in the liver and kidney was not excessive, and hypercholesteremia was not present in the parents.

During the hospital course, the symptoms of the disease increased. This may have been associated with an increased strain on the already impaired carbohydrate metabolism from the apparently low grade infection of the upper respiratory tract.

Death in this case seemed directly attributable to secondary infection, the commonest cause for deaths in the reported cases.

Although the disease is not as rare as was first believed, there is no other case recorded in the files of the Rhode Island Hospital from Jan. 1, 1934 to Jan. 1, 1942; during that period there were 5,282 admissions to the pediatric service. The chief differential diagnoses to be considered are fatty liver, hepatic tumor and, less commonly, early cirrhosis. There has not been enough observation of the cases so that any definite statements can be made as regards prognosis, but it is by no means hopeless. In most of the cases coming to autopsy death has been caused by intercurrent infection. Treatment has apparently nothing specific to offer. Some of the records state that the patient had preference for starchy foods, and in some cases recurrent attacks of vomiting that have occurred have been more or less relieved by frequent feedings of carbohydrates. Van Creveld [8] stated that he could not evaluate the influence that increased intake of carbohydrate may have on increasing the storage of glycogen.

SUMMARY

The case of a 14 month old boy is reported for whom clinically, by laboratory examination and by autopsy a diagnosis of glycogen disease of the hepatomegalic type (von Gierke's disease) was made. In this case the glycogen of the liver apparently was not abnormal, but the glycogen metabolism was deranged, as shown by deficient storage of ingested dextrose, inability to mobilize dextrose from large amounts of glycogen in the liver when epinephrine was injected, ketonuria and failure of hepatic glycogenolysis after death.

Assistance in this study was given by Dr. B. Earl Clarke and Dr. Harold W. Williams, who made the reports of the biopsy and the pathologic examinations; by Dr. Eske Windsberg, who performed the biopsy of the liver; by Dr. William P. Buffum and Dr. Henry E. Utter, chiefs of the services to which the child was admitted, and by Dr. Harold G. Calder, who referred the child to the hospital.

Rhode Island Hospital.

BACILLUS ALCALIGENES BACTEREMIA COMPLICATING DIABETES MELLITUS

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From the standpoint of medical bacteriology, micro-organisms may be divided into two large groups, namely, pathogenic and nonpathogenic bacteria and viruses. In many instances it is possible to prove the pathogenicity of a micro-organism by fulfilling all or some of Koch's postulates. On the other hand, it is a recognized fact that so-called nonpathogenic bacteria may occasionally cause disease in man and in animals. It is also established beyond doubt that certain bacterial species may be nonpathogenic at one particular site, for instance, in the intestinal tract or on the skin, and may become pathogenic when present in other organs and organ systems.

Bacillus alcaligenes is generally considered to be nonpathogenic for man. There are available, however, a number of reports indicating that this species may cause infections in man. We should like to present observations on a case of Bacillus alcaligenes bacteremia complicating diabetes mellitus.

REPORT OF A CASE

A. G., a white girl 11 years and 5 months of age, was admitted to the Children's Hospital (Dr. Douglas P. Arnold, chief of staff) on Nov. 18, 1942. Her past history revealed nothing of importance, except that according to her parents she had been suffering from diabetes mellitus for about one year but was not under the care of a physician during that time. Two weeks prior to admission two teeth were extracted because of abscesses. The face adjacent to the extraction began to swell five days before entrance. The afternoon of admission she became weak and dizzy; during the night she was extremely thirsty and became irrational and finally lapsed into a comatose condition.

When seen on entrance at 11:55 the same night her temperature was 103 F. and the pulse rate 170 per minute. She was a well nourished child. Her respirations were rapid, regular and deep. There was a strong sweet fruity odor to the breath. The skin was dehydrated but warm. The right jaw was greatly swollen. The eyeballs were soft. The pupils were round and regular and reacted to light. The tongue was dry and coated. In the mouth, particularly on the right side, there was blood and pus. Purulent material was issuing from a longitudinal area of incision about 1.5 cm. in length and 0.5 mm. in width along the gingival margin on the right mandible. The lungs were normal. The heart tones were of fair quality and the rhythm regular. The blood pressure was 110 systolic and 70 diastolic. Knee and ankle jerks and abdominal reflexes could not be elicited.

A specimen of urine obtained on admission revealed a specific gravity of 1.022, a slight amount of albumin, large quantities of sugar and approximately 1 to 3 granular casts per high power field. Ketone bodies were present. Examination of the blood showed 18 Gm. of hemoglobin and 27,900 leukocytes, with 69 per cent filaments, 29 per cent band cells and 2 per cent lymphocytes. The blood sugar content was 944 mg. per hundred cubic centimeters; the carbon dioxide-combining power of the blood 8 volumes per cent. A tuberculin test with 0.1 mg. of old tuberculin elicited a negative response. A Kahn test gave a negative reaction.

From the time of her admission until 9:30 a. m. the following day, the patient received a total of 140 units of regular insulin subcutaneously. She also was given isotonic solution of sodium chloride intravenously by drip during the night. At the end of that time the blood

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sugar level was 47 mg. per hundred cubic centimeters and the carbon dioxide–combining power of the blood plasma 19 volumes per cent. Therefore, the infusion was changed to 5 per cent dextrose in solution of sodium chloride. The hydration gradually improved, and the patient became responsive and more alert by the middle of the next afternoon, at which time the ketone bodies in the urine disappeared. At the same time she was fully awake, responded to questions and retained fluid by mouth.

The swelling under the right mandible gradually became localized and fluctuant. A roentgen examination of the mandible revealed nothing abnormal. An incision was carried out with the area under local anesthesia. Foul, purulent material was obtained. A culture from the lesion revealed hemolytic streptococci, Staphylococcus aureus and an anaerobic gram-positive bacillus. A blood culture taken the day of the operation remained sterile.

On November 21 the patient was given sulfathiazole by mouth, and this treatment (total of 78 Gm.) was continued until December 7.

The temperature gradually returned to normal. However, on November 29 it began to rise slightly, approaching 100 F. and then 101 F. and reached 104 F. on December 1. The temperature spiked daily during the following six days and at times was as high as 104 F. Then the temperature dropped to normal. On December 10 the submaxillary abscess, which had ceased to drain and had become progressively larger, spontaneously began to drain again. Considerable amounts of purulent material were released. The drainage gradually subsided, and the wound healed.

On December 14 the temperature again rose above normal and reached 104 F. on the following day. It was spiking for forty-eight hours. Blood for culture was taken on December 15, and the culture revealed the presence of approximately 200 colonies of Bacillus alcaligenes faecalis per cubic centimeter of blood. The blood culture was repeated on December 17 and again showed many colonies of the same micro-organism. A culture of blood taken on December 18 showed 3 to 4 colonies of the identical bacillus. Subsequent blood cultures (Dec. 22 and 29 and Jan. 4, 1943) remained sterile. The temperature became normal on December 17 and, with the exception of an increase to 103 F. on January 3 and 4, remained normal up to the time of discharge, on January 10.

During the period when the patient's blood contained B. alcaligenes, the insulin requirement rose from 76 to 88 units of regular insulin in twenty-four hours. When the cultures became negative, the insulin requirement dropped rapidly. At the time of discharge the patient was receiving 22 units of protamine insulin daily.

In order to determine whether or not the patient developed antibodies against the strain of B. alcaligenes isolated on three occasions from the blood, her serum was tested for the presence of agglutinins. The results of the experiments were entirely negative in spite of the fact that the patient's own strain was used as antigen, the agglutination tests were carried out both at 37 C. and at 55 C., the mixture of serum and bacterial suspension was centrifuged and the patient's serum was examined up to twenty-one days after the infection of the blood stream had occurred. It may be mentioned also that the negative results were not due to a zone phenomenon, since serum in dilutions up to 1:1,000 failed to cause agglutination.

COMMENT

A review of the literature pertaining to the potential pathogenicity of B. alcaligenes reveals that this micro-organism may cause a variety of different clinical syndromes. In the first place, it was considered to be the causative agent of typhoid-like fever. Cases of such a disease were reported by numerous authors, including Petruschky, Altschüler, Lafforgue, DeMagalhaes, Watson and Row. The literature on the subject was thoroughly reviewed in 1927 by Wyatt,[1] who added a case of his own, and in 1938 by Goldberg.[2] At the present time, it is extremely difficult to determine whether all the cases reported many years ago actually represent infections caused by B. alcaligenes. The possibility exists that this micro-organism was a secondary invader, a contaminant or a saprophyte,

1. Wyatt, W. S.: Bacteremia Due to Bacillus Fecalis Alkaligenes, with Report of a Case, Am. J. M. Sc. **174**:181-191 (Aug.) 1927.

2. Goldberg, L. H.: Bacillus Alcaligenes Infections, New York State J. Med. **38**:122-126 (Jan. 15) 1938.

particularly in those cases in which it was isolated from the feces. On the other hand, the evidence presented in some of the communications supports the assumption of the pathogenicity of B. alcaligenes. This holds true especially in cases in which this micro-organism was recovered from the blood and, as in the case of Petruschky, from rose spots. Moreover, some of the patients developed specific agglutinins in high titer during the illness. For instance, in the case reported by Lafforgue the titer of agglutinins against B. alcaligenes was 1:150; in the case of DeMagalhaes, 1:400, and in Wyatt's case, 1:150. It is worth noting that this titer of agglutinins is definitely above normal. Recently, several well studied cases in which there was a typhoid-like picture were reported by Andrieu and associates [3] and by Girolami.[4] B. alcaligenes was isolated from the blood of the patients. The serums agglutinated the organism in titers of 1:500, 1:400 and 1:600 respectively, and failed to agglutinate typhoid and paratyphoid bacilli. The patients recovered.

A second group of patients whose illness apparently was caused by B. alcaligenes presented the features of septicemia or bacteremia. McIntyre,[5] and Voorhies and Wilen [6] recently reported such cases. The illness in the case of Voorhies and Wilen lasted for four months and was characterized by complicating polyarthritis and meningitis. It seems likely that in some of these cases the infection resembled those caused by other micro-organisms which usually are saprophytic but potentially pathogenic, namely, Bacillus coli, Bacillus alcalescens, Bacillus proteus, Bacillus pyocyaneus and others.

B. alcaligenes may cause localized infections as well, such as inflammatory lesions in the urinary tract, purulent meningitis (Gatewood,[7] Mason [8] and Kutscher [9]) and abscesses (Pohl and Raymond [10]), and it may be encountered in the peritoneal exudate in patients with perforation of the intestine. B. alcaligenes has been recovered also from gallstones [11] and as the organic nucleus in renal calculus.[12] In 1931, Barrow [13] reported an epidemic of conjunctivitis which in his opinion was due to B. alcaligenes. This outbreak occured in a training ship for men in the Royal Navy and the Merchant Service. The possibility,

3. Andrieu, G.; Crosnier, R., and Moutier, P.: Les septicémies à Bacillus foecalis alcaligenes, Paris méd. **1**:506-508 (June 6) 1936.

4. Girolami, M.: Sulla patogenicità del "Bacillus foecalis alcaligenes" nell'uomo; studio clinico e bacteriologico, Arch. per le sc. med. **64**:665-680 (Dec.) 1937.

5. McIntyre, C. A.: A Case of Blood Stream Infection with "Fecalis Alkaligenes" and Marked Hepatitis, Mil. Surgeon **79**:140-143 (Aug.) 1936.

6. Voorhies, N. W., and Wilen, C. J.: Alcaligenes Faecalis Bacteremia, Am. J. M. Sc. **204**:719-723 (Nov.) 1942.

7. Gatewood: Bacillus Fecalis Alkaligenes Meningitis, Am. J. Surg. **12**:435-436 (June) 1931.

8. Mason, R. J.: Acute Meningitis Due to Bacillus Fecalis Alcaligenes, J. Pediat. **4**:514-516 (April) 1934.

9. Kutscher, G. W., Jr.: Alkaligenes Bookeri Meningitis: Review of Literature on Gram-Negative Bacillus Meningitis, Arch. Pediat. **54**:610-616 (Oct.) 1937.

10. Pohl, C., and Raymond, S. W.: Bacillus Fecalis Alcaligenes Abscess, J. Internat. Coll. Surg. **4**:547 (Dec.) 1941.

11. Daniel, W. W., and Greene, E. H.: Recovery of Bacillus Fecalis Alkaligenes from Gall-Stones, South. M. J. **22**:977-980 (Nov.) 1929.

12. Stuart, G.; Thompson, W. E., and Krikorian, K. S.: Bacillus Alkaligenes Faecalis as Organic Nucleus in Renal Calculus, Brit. J. Urol. **6**:243-247 (Sept.) 1934.

13. Barrow, R. H. B.: An Epidemic of Conjunctivitis Due to Infection with Bacillus Faecalis Alkaligenes, Brit. J. Ophth. **15**:319-323 (June) 1931.

however, has to be considered that this infection may have been caused primarily by a virus and that B. alcaligenes merely was a secondary invader.

In the present case B. alcaligenes can be considered as the causative agent of the systemic infection. It was isolated from the blood of the patient on three different occasions, and no other micro-organisms were found in the blood.

The strain had the characteristics of Alcaligenes faecalis. It grew readily on plain agar and Endo agar. It failed to produce acid from dextrose, lactose, sucrose, rhamnose, maltose, mannitol, xylose and dulcitol. Indole was not produced, and gelatin was not liquefied. Prof. H. J. Conn, chief in research, New York State Agricultural Experiment Station, Geneva, N. Y., examined the strain. He reported as follows: "[The strain] proves much more like the intestinal inhabitants, which I think are probably Alcaligenes faecalis, than like my soil forms or those cultures from the American Type Culture Collection on which my first studies were based. It seems to require organic nitrogen in order to grow. It produces carbon dioxide in glucose-peptone broth, but without causing an acid reaction. That does not say that it is Alcaligenes faecalis, however, because of the confusion in regard to these organisms and their similarity, from the standpoint of physiology, to certain forms of Brucella, as for example Brucella bronchiseptica." With respect to the present day state of this micro-organism reference is made to Conn's paper.[14]

It is interesting to note that the bacteremia apparently was self limited and disappeared without administration of a chemotherapeutic agent such as a sulfonamide compound. In the case reported by Voorhies and Wilen[6] the symptoms disappeared and the blood became sterile after the use of sulfadiazine. An investigation into the antibody response of our patient failed to reveal positive results. Over a period of three weeks following the onset of the bacteremia the serum of the patient was examined for the presence of agglutinins, with entirely negative results. The failure to demonstrate antibodies against B. alcaligenes was not due to a zone phenomenon, since negative results were obtained with serum in dilutions ranging from 1:10 to 1:1,000. Furthermore, it should be noted that the test tubes containing serum and bacterial suspension were centrifuged, in view of the observation of Zeithaml and Ecker[15] that specific agglutination can be obtained by this procedure with Sonne dysentery bacilli which otherwise were not agglutinated. It also may be mentioned that the agglutination tests were carried out at both 37 and 55 C.

It is well known that patients suffering from diabetes mellitus are more apt to acquire infections than healthy persons. To the best of our knowledge this case represents the first instance of a B. alcaligenes bacteremia complicating diabetes mellitus with coma. In this connection it is interesting to note that Bowen and Witebsky[16] described 4 cases of septicemia in women with diabetes. B. coli was the causative agent in 3 cases and B. aerogenes in the remaining one. These cases presented an acute onset and rapid course. The diseaese ended fatally in 3 cases. The authors discussed the differentiation between diabetic coma and a state of drowsiness and sleepiness caused by the infection. The present case differs from those reported by Bowen and Witebsky inasmuch as true diabetic

14. Conn, H. J.: Validity of the Genus Alcaligenes, J. Bact. **44**:353-360 (Sept.) 1942.

15. Zeithaml, C. E., and Ecker, E. E.: Relative Inagglutinability of Castellani-Sonne Group of Dysentery Bacilli, Proc. Soc. Exper. Biol. & Med. **31**:26-28 (Oct.) 1933.

16. Bowen, B. D., and Witebsky, E.: Fulminating Bacillus Coli Septicemia in Women with Diabetes, Arch. Int. Med. **67**:1099-1106 (June) 1941.

coma was present and the infection was not responsible for the unconsciousness of the patient.

SUMMARY

A case of infection of the blood stream by Alcaligenes faecalis complicating diabetes mellitus is presented. The bacteremia was self limited and disappeared without treatment with a sulfonamide compound. No agglutinins were formed during the illness. B. alcaligenes as a potential pathogen is discussed.

219 Bryant Street.

Progress in Pediatrics

PANCREATIC FUNCTION AND DISEASE IN EARLY LIFE

III. METHODS OF ANALYZING PANCREATIC ENZYME ACTIVITY

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Recent studies of the celiac syndrome have led to the separation of a group of patients with a clinical picture similar in many respects to that of idiopathic celiac disease.[1] The terms cystic fibrosis of the pancreas and pancreatic fibrosis have been used to describe the pathologic state in the pancreas. In these patients, pancreatic achylia or hypochylia has been demonstrated as a constant and characteristic finding, in contrast to the relatively normal values in idiopathic celiac disease.[2] Indeed, analysis of activity of pancreatic enzymes in the duodenal content has become the most reliable method of differentiation between these two diseases. The greatest value of this procedure has been found in establishment of proof of the existence of pancreatic fibrosis in infants under 12 months of age in whom symptoms involving the respiratory system obscure the nutritional aspect of the disease.[3] For the convenience of those who may conduct studies of pancreatic enzymes in infants and children, this description of methods used originally by others is given in some detail, with a critical evaluation based on an experience gained from analysis of the duodenal drainage obtained from more than 150 infants and children. Reference may be made to the recent description of methods by Andersen,[1b] who kindly demonstrated those she used in her studies to one of us (C. L. M.). The authoritative critique of methods by W. C. Davison [4] should be consulted by the interested worker. The account which follows describes the procedures as used in our studies.[5]

These studies were supported by a grant from the Ann Proctor Rice Fund, of Harvard Medical School.

From the Children's Hospital and the Infants' Hospital, Boston, and the Department of Pathology, Harvard Medical School.

1. (*a*) Andersen, D. H.: Cystic Fibrosis of the Pancreas, Vitamin A Deficiency and Bronchiectasis, J. Pediat. **15**:763, 1939; (*b*) Pancreatic Enzymes in the Duodenal Juice in the Celiac Syndrome, Am. J. Dis. Child. **63**:643 (April) 1942. (*c*) Farber, S., and Maddock, C. L.: The Relation of the Pancreas to the Celiac Syndrome, Am. J. Path. **17**:445, 1941. (*d*) Farber, S.; Shwachman, H., and Maddock, C. L.: Pancreatic Enzyme Activity and the Celiac Syndrome, J. Clin. Investigation, to be published, November 1943.

2. Andersen.[1b] Farber and Maddock.[1c] Farber, Shwachman and Maddock.[1d]

3. Andersen.[1b] Farber, Shwachman and Maddock.[1d]

4. Davison, W. C.: Difficulties in Enzymic Titration of Duodenal Contents, Bull. Johns Hopkins Hosp. **70**:504, 1942.

5. (*a*) Farber, Shwachman and Maddock.[1d] (*b*) Maddock, C. L.; Farber, S., and Shwachman, H.: Pancreatic Function and Disease in Early Life, The Effect of Secretin on Pancreatic Function of Infants and Children, Am. J. Dis. Child., this issue, p. 370.

METHODS

Collection of Fluid.—The duodenal content was collected from patients and normal infants and children after a preliminary fasting period of at least nine hours. The collection was made usually in the morning about 10 o'clock. Acutely ill, dehydrated or febrile patients were not subjected to this examination. The previously sterilized Levin duodenal tube was introduced through the nostril. A no. 10 French (3.5 mm. in diameter) tube was employed for small infants and a no. 12 French (4 mm. in diameter) tube for older infants and children. This soft rubber tube is approximately 4 feet (120 cm.) long and has four orifices within the terminal 2 inches (5 cm.). Equally satisfactory was a smooth rubber tube with a 1/16 inch (1.6 mm.) or 3/32 inch (2.4 mm.) lumen with a 1/32 inch (0.8 mm.) wall cut to any specified length, with as many orifices as desired at the terminal end.

The tube should be discarded when it has lost its elasticity. The gastric contents were aspirated and the tube gently guided into the duodenum under fluoroscopic visualization. When the terminal tip was approximately 2 inches (5 cm.) beyond the pylorus, the tube was anchored to the face with a narrow strip of adhesive tape. If too much slack was permitted in the stomach, and as a result the tube became coiled or looped, the tip of the tube often advanced far below the ampulla of Vater. Less difficulty was encountered in passage of the tube in infants than in older children. The procedure required from five to thirty minutes, with the average time around fifteen minutes. Only rarely was there great difficulty encountered in passage of the tube into the duodenum. The appearance of an alkaline bile-colored fluid was used as an indicator of the proper position of the tube. The fluid was collected by gravity or gentle suction with a syringe in ten to thirty minute periods for one to three hours, the time required depending on the rate of flow. The specimen was placed immediately in an ice bath. In the case of older children an occasional mass of mucus or gastric contents appeared, and this portion of the material was discarded. Constant observation during the collection, therefore, was necessary. A record was made of the volume of fluid collected in each of the separate specimens, the time of collection of each sample, the color, the p_H and finally the viscosity. The amount of duodenal fluid necessary for a complete duplicate determination of the activity of the three enzymes is approximately 5 cc.—3 cc. for lipase, 0.5 cc. for trypsin and 0.5 cc. for amylase.

Analysis of Duodenal Content.—The duodenal content was kept in an ice water bath and analyzed the day of collection. The p_H was determined colorimetrically with the aid of Clark and Lub indicators. The lipolytic, tryptic and amylolytic activities were quantitated as follows:

In the determination of lipase the method of Willstätter, Waldschmidt-Leitz and Memmen was employed with slight modification.[6] The substrate was olive oil (Laco brand with saponification no. 193). An aminoacetic acid buffer of p_H 8.9 was substituted for the one employed by these authors. A freshly prepared 3 per cent solution of egg albumin served as an emulcent and a 2 per cent solution of calcium chloride as the activator. To 2.5 Gm. of olive oil in a glass-stoppered Erlenmeyer flask were added 2 cc. of the aminoacetic acid buffer, 0.5 cc. of the solution of calcium chloride, 0.5 cc. of the solution of albumin and finally 10 cc. of a 1:10 dilution of the duodenal juice to be analyzed. After it had been shaken vigorously for three minutes at 37.5 C. in the water bath, the mixture was kept at this temperature for one hour, the total period of incubation being one hour and three minutes. The reaction was then terminated by the addition of 35 cc. of an alcohol-ether mixture (4 parts of 95 per cent alcohol and 1 part of ether). The determinations were carried out in triplicate, with the third determination as the control, since enzymatic activity in it was inhibited by the immediate addition of the alcohol-ether mixture. The fatty acids liberated were then titrated against tenth-normal alcoholic potassium hydroxide, thymol blue being used as indicator. The number of cubic centimeters of alcoholic potassium chloride required to bring the control to a distinct blue varied slightly from 3.3 to 3.6 cc. in different samples of duodenal fluid. This control value was subtracted from the number of cubic centimeters of potassium hydroxide required previously mentioned. A lipase unit is defined as that amount of lipase which under the given conditions would split 24 per cent of 2.5 Gm. of olive oil. The calculation is made as follows: $\frac{\text{Cc. of 0.1 N KOH}}{20.7} \times 100 = \text{units/100 cc.}$ The constant (20.7) is obtained as follows: The saponification number of olive oil is 193, which means that 193 mg. of potassium hydroxide is needed to hydrolyze completely 1 Gm. of olive oil. $\frac{24}{100} \times 193 \times 2.5 = 116$ mg. KOH. This would be equivalent to 1 unit, and since 5.61 mg. of potassium hydroxide is equivalent to 1 cc. of tenth-normal solution of potassium hydroxide, and $\frac{116}{5.61} = 20.7$, 20.7 cc. of the tenth-normal solution is equivalent to 1 unit.

6. Willstätter, R.; Waldschmidt-Leitz, E., and Memmen, F.: Bestimmung der pankreatischen Fettspaltung, Ztschr. f. physiol. Chem. **125**:93, 1923.

In a few instances a second determination was carried out with use of a different substrate—an olive oil emulsion recommended by Comfort and Osterberg [7] for serum lipase and marketed by the Abbott Laboratories (list no. 6111). The values obtained by this method were uniformly higher. The impression is gained that this substrate permitted greater activity because of the more satisfactory state of emulsification.

Considerable variation in lipolytic activity occasionally was encountered in different specimens of duodenal juice obtained either during one collection period or at a later date from the same patient. Some of the variability in results may be explained by the variation in concentration and presence of bile, intestinal and pancreatic juice, the state of emulsification of the reaction mixture or the constant liberation of free acid which may progressively inhibit the reaction. The clinical usefulness of this method, however, is unimpaired by these technical difficulties, allowance for which may be made if their significance is recognized.

Tryptic activity was determined viscosimetrically by use of an adaptation of the method employed by Waksman and Davison.[8] A 3 per cent phosphate-buffered gelatin [9] solution of p_H 7.4 served as the substrate. The Ostwald type of viscosimeter tube with a capacity of 5 cc. was employed, the determination being conducted in a water bath kept at a temperature of 37.5 C. The viscosity of the substrate was approximately two and one-half times the viscosity of water. The determinations were carried out in pairs as follows: To 10 cc. of the substrate heated to 37.5 C. 1 cc. of the diluted duodenal juice was added, and after these had been mixed, 5 cc. was immediately placed in each of two viscosimeter tubes. The initial viscosity was determined, usually within three minutes after the enzyme had been added to the substrate. Further readings were made at about three to five minute intervals until a drop of approximately 20 per cent in the initial viscosity was obtained. The duodenal juice was diluted in such a manner that this change in viscosity occurred between twenty and sixty minutes. In fluids from normal persons this requirement was met by a 1:100 to 1:150 dilution of the original juice. When the duodenal juice contained no trypsin, of course there was no change in viscosity.

A unit of trypsin is defined as that amount of enzyme required to reduce the initial viscosity of the substrate-enzyme mixture 20 per cent in one hour.

The choice of dilution of the duodenal fluid for the assay of trypsin may introduce some error into the expression of the final result. The error may be negligible, however, as is demonstrated in chart 2, which shows the tryptic activity in the duodenal content of a normal patient at three different dilutions. In each case the 20 per cent drop in viscosity of the substrate occurred between twenty minutes and one hour. In the 1:100 dilution the calculated activity is 214 units, in the 1:150 dilution 208 units and in the 1:200 dilution 256 units.

The substrate was prepared in a relatively large bulk, which lasted fully a year in its concentrated form when stored in the refrigerator. From this was prepared the working solution of 3 per cent gelatin-buffered substrate, which lasted from two to four months. The constancy of the substrate was checked from time to time with a 1:5,000 standard solution of pancreatin and fell usually within 5 to 10 per cent of that of the original solution. This variation in substrate should be recognized in an analysis of results, since it accounts for a large amount of the error in the method.

The tryptic activity should be determined soon after the collection of fluid. In 3 instances we compared the tryptic activity at the end of twenty-four hours, when the fluid had been kept at room temperature, with that in fresh fluid. There was a drop in activity to 48 per cent, 50 per cent and 60 per cent of the original levels. When the fluid had been stored in the refrigerator overnight, however, the loss in activity was practically nil in 2 instances, was 5 per cent and 6 per cent in 2 other instances and 24 per cent of the original in still another instance. In no case did we find autoactivation of a fluid collected from a patient with pancreatic fibrosis when the fluid was kept on ice or stored at room temperature.

Of the many factors that affect the expression of the final result when the viscosimetric method is used, the rate of change in the viscosity of the substrate is one of the most important. The accompanying chart illustrates this point (chart 1). Each curve is made by calculating the activity of the fluid at different stages of the reaction. A change of 20 per cent of the initial viscosity should occur in between twenty and sixty minutes. Examination of curve 2, for example, shows that when twenty-four minutes is taken as the time for the end point a result of 212 units is obtained. When the end point is taken at thirty-eight minutes,

7. Comfort, M. W., and Osterberg, A. E.: Lipase and Esterase in the Blood Serum: Their Diagnostic Value in Pancreatic Disease, J. Lab. & Clin. Med. **20**:271, 1934.

8. Waksman, S. A., and Davison, W. C.: Enzymes, Baltimore, Williams & Wilkins Company, 1926.

9. Peter Cooper's clarified gelatin, Gowanda, N. Y.

the result is 175 units. There is, thus, a difference of 37 units, depending on the time at which the end point is taken. In this case there was a 17 per cent change of the original viscosity at twenty-four minutes, and a 22 per cent change was noted at the end of thirty-eight minutes. The 20 per cent change occurred after thirty-three and eight-tenths minutes. The activity is, therefore, 184 units.

Curves 1 *A* and 1 *B* are included to show the result of duplicate determinations on 2 specimens of duodenal juice. In the case of 1 *A* and 1 *B* the slope of the curve is fairly steep, and the two curves are nearly superimposed. If 1 *A* is examined it is found that at the end of forty-four and two-tenths minutes there is a 19 per cent change in original viscosity, with the calculated activity at 63.0 units, whereas at the next reading, at the end of fifty-one and eight-tenths minutes, with a change in viscosity of 20.4 per cent of the original value, the activity now becomes 58.8 units. Since the 20 per cent change occurred at the end of forty-nine and five-tenths minutes (by extrapolation), the final activity becomes 60 units. In the check or duplicate run the activity was found to be 63 units. In contrast to the previous illustration the calculation becomes less inaccurate as the slope of the curve of activity increases.

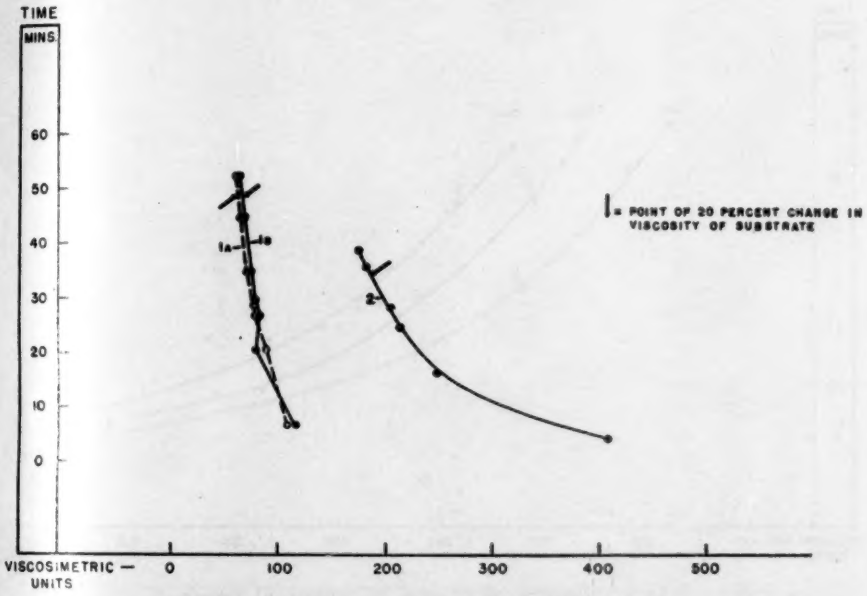

Chart 1.—Relation of time to end point in viscosimetric method.

A variety of methods has been used to determine the proteolytic activity of pancreatic juice. Although the viscosimetric method is adequate, a still cruder method, which would lend itself more readily to routine hospital laboratory work, would be satisfactory from the point of view of the clinician who is faced with the problem of differentiating pancreatic fibrosis from other conditions. With this in view, one of us (H. S.) has employed a gelatin film method (one side of an x-ray film is scraped, and the other side serves as the substrate). Tryptic activity is measured by the use of graded dilutions of duodenal juice. One drop of each dilution is placed on the film, which is incubated at 30 C. for thirty minutes. The film is then washed in a stream of cold water. A clear spot indicates liquefaction of the gelatin film. The juice from a normal patient may be active in a dilution of 1:30 to 1:40, whereas no significant change is produced in a 1:2 or 1:4 dilution of juice from a patient with pancreatic fibrosis. What appears to be a more accurate and yet simple method is an adaptation of the recent modification of the original Fermi method by Andersen and Early.[10]

This method is based on the fact that gelatin when subjected to enzymatic hydrolysis changes its properties so that it no longer solidifies at refrigerator temperature. The amount of enzyme necessary to bring about this change is quantitatively determined.

10. Andersen, D. H., and Early, M. V.: Method of Assaying Trypsin Suitable for Routine Use in Diagnosis of Congenital Pancreatic Deficiency, Am. J. Dis. Child. **63**:891 (May) 1942.

The substrate is prepared as follows:

Pour the contents of two envelopes of Knox gelatin (15 Gm.) into a 250 cc. beaker. Dissolve in lukewarm water (about 100 to 150 cc.), adding water in small amounts (20 cc.), with constant stirring to keep the mixture free from lumps. Pour into a 200 cc. volumetric flask and bring the volume up to 200 cc. with addition of warm water. Mix and allow to stand in water until a uniform solution is produced. Transfer to an Erlenmeyer flask for storage, and add about 2 crystals of thymol as a preservative. Keep on ice. This solution may be used as long as two months after preparation.

A 1:10 and a 1:100 dilution of the duodenal juice to be analyzed is prepared; a 5 per cent solution of sodium bicarbonate is used as the diluting fluid. To a series of tubes are added varying amounts of the duodenal fluid: to tubes 1, 2, 3 and 4, 0.125 cc., 0.25 cc., 0.5 cc. and 1.0 cc., respectively, of the 1:100 dilution; to tubes 5, 6, 7 and 8, 0.2 cc., 0.4 cc., 0.8 cc. and 1.6 cc., respectively, of the 1:10 dilution.

The volume in each tube is adjusted to 2 cc. by the addition of a 5 per cent solution of sodium bicarbonate. Two cubic centimeters of gelatin previously warmed at 37 C. is added to each tube, and after the contents have been thoroughly mixed, it is incubated in a water

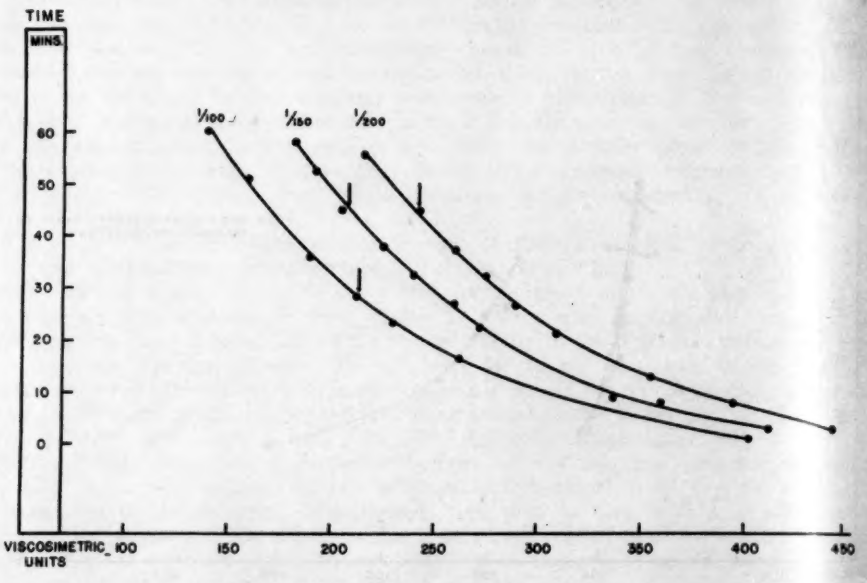

Chart 2.—Relation of dilution to activity of trypsin.

bath at 37.5 C. for one hour. The reaction is stopped immediately if the tubes are placed at refrigerator temperature. The gelatin which has not been acted on will solidify at the end of one to two hours, when the final reading may be made. The first tube in the series that shows appreciable liquefaction is taken as the end point. The end point of a normal duodenal fluid may be 0.25 cc. of a 1:100 dilution, whereas 0.15 cc. or more of undiluted fluid from a patient with pancreatic fibrosis may cause no liquefaction. This method has been employed also in the analysis of extracts of pancreatic tissue.

Twenty-three determinations were made on the duodenal content obtained from 14 patients to permit a comparison of the viscosimetric method and the Andersen-Early modification of the Fermi method for determination of tryptic activity. The results plotted on chart 3 show a consistent agreement. A value of 0.005 given by the Andersen-Early method, for example, may be correlated with values from 200 to 350 units obtained by the viscosimetric method. This spread, while apparently great, is of little significance, since an amount of activity of 200 units represents sufficient tryptic activity to be regarded as normal. Excellent correlation, too, was observed at the level of 100 units given by the viscosimetric method. When there was no tryptic activity demonstrable by this method, none was found by the Andersen-Early method.

To provide a simple method of reporting the amount of tryptic activity in the duodenal drainage we have adopted the suggestion of Dr. Alfred Shohl and have compared in the table the values obtained by the modified Fermi method and those obtained by the viscosimetric

Comparison of the Trypsin Content of Duodenal Juice Determined by the Fermi Method and by the Viscosimetric Method and Calculated in Percentage of the Enzyme Content of the Juice of Normal Infants

Tube	Fermi Method, Cc. of Juice	Viscosimetric Method, Units per Cc.	Percentage of Normal (100% = 250 Units)
1 (control)	0.0	...	...
2	0.0025	400	160
3	0.005	250	100
4	0.01	130	55
5	0.02	75	35
6	0.04	40	20
7	0.08	25	10
8	0.16	15	5

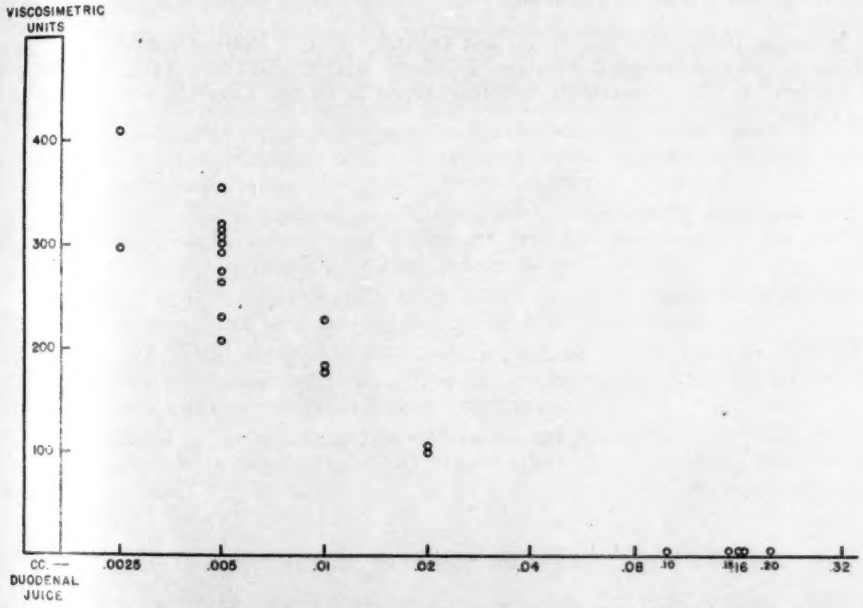

Chart 3.—Correlation of viscosimetric and Fermi methods of determination of trypsin, as modified by Andersen and Early.[10]

method, with the percentage of normal values calculated on the assumption that 250 units of trypsin (viscosimetric method) represents the average for the normal infant or child.

The activity of amylase also was determined viscosimetrically with the aid of the same technic as that used for trypsin.[11] The unit of activity is defined in the same way. The starch substrate was prepared according to the method of Thompson, Tennant and Wies, with the exception that 5 Gm. of starch instead of 3 Gm. was used.[12] To 5 Gm. of Eimer and Amend soluble starch were added 15 cc. of 1 molar solution of sodium acetate and 45 cc. of distilled water. After it had been cleared by gentle heating, the solution was

11. (*a*) Davison, W. C.: A Viscometric Method for the Quantitative Determination of Amylase, Bull. Johns Hopkins Hosp. **37**:281, 1925. (*b*) Thompson, W. R.; Johnson, E., and Hussey, R. G.: A Viscosimetric Method of Estimation of Enzyme Concentration with Special Reference to Amylase, J. Gen. Physiol. **15**:1, 1931.

12. Thompson, W. R.; Tennant, R., and Wies, C. H.: Studies in Starch Amylase Viscosimetry: I. A Sensitive Precision Method for the Estimation of Amylolytic Activity Applicable to Human Serum, J. Biol. Chem. **108**:85, 1934.

autoclaved at a pressure of 18 pounds (8 Kg.) for twenty minutes and then added to 10 cc. of a 10 per cent solution of calcium chloride in 0.15 molar solution of sodium acetate and 0.05 molar solution of acetic acid. The solution was made up to a volume of 100 cc. with hot distilled water and filtered in an oven at 57 C. The clear filtrate was adjusted to a p_H of 6.8. This substrate was made fresh approximately every eight to ten days. As in the case of trypsin, there is an appreciable loss of activity when the fluid is stored overnight at room temperature.

In carrying out the analysis for amylolytic activity on fluids from patients under 4 months of age a 1:10 dilution of the duodenal content was made. For older infants and children the dilution employed was that usually used in the analysis of tryptic activity. It is advisable to make these dilutions immediately before they are used.

Rothman, Widener and Davison have published recently their observations on the optimal reaction for the starch-liquefying activity of duodenal amylase of infants as determined viscosimetrically.[13] They concluded that the optimal p_H of the reaction at 34 C is 6.9 to 7.0 when starch suspensions in twentieth-molar phosphate buffer solutions are used. Our observations were made with use of an acetic acid buffer at a p_H of 6.8, with the reaction mixture at 37.5 C. Davison pointed out that contamination of the duodenal fluid with gastric juice may accelerate the starch-liquefying activity as determined viscosimetrically.[14]

300 Longwood Avenue (Dr. Farber).

13. Rothman, P. E.; Widener, D. C., and Davison, W. C.: Optimal Reaction for Starch-Liquefying Activity of Duodenal Amylase of Infants, Am. J. Dis. Child. **64**:237 (Aug.) 1942.

14. Davison, W. C.: Amylase-Accelerating Action of Gastric Contents, Am. J. Dis. Child. **63**:728 (April) 1942.

Abstracts from Current Literature

Biochemistry; Bacteriology, and Pathology

EFFECT OF MANGANESE ON CALCIFICATION IN THE GROWING RAT. CHARLOTTE CHORNOCK, N. B. GUERRANT and R. ADAMS DUTCHER, J. Nutrition **23**:445 (May) 1942.

Chornock, Guerrant and Dutcher in their studies with rats, noted that high manganese intake retarded growth and caused pronounced interference with phosphorus retention, more than that of calcium. Low intakes of manganese did not retard growth and showed little or no effect on bone calcification with either a normal or a rachitogenic diet.

ROBERT C. FREDEEN, Kansas City, Mo.

AN IN VITRO STUDY ON THE SYNERGISTIC ACTION OF SULFAMIDO COMPOUNDS AND AZOCHLORAMID UPON VARIOUS PATHOGENIC MICROORGANISMS. ERWIN NETER, J. Pharmacol. & Exper. Therap. **74**:52 (Jan.) 1942.

The author cites the common clinical experience that the sulfonamide drugs are not usually very effective against localized purulent lesions and certain subacute and chronic infections. This fact has been thought to be due to the inhibiting action of the organic materials in the inflammatory site. Experiments were made with combinations of sulfonamide drugs in broth cultures with azochloramid (N,N'-dichloroazodicarboxamidine), a relatively stable bacteriostatic and bactericidal chlorine compound whose effectiveness in the presence of organic matter is inhibited to a slight degree only. The results are as follows:

"1. Azochloramid used in combination with sulfanilamide, sulfathiazol, and sulfadiazine may exert greater bacteriostatic activity toward Group A hemolytic streptococcus than does either compound alone in like or somewhat higher concentrations.

"2. A slight increase in bacteriostatic activity toward Group D hemolytic streptococcus was obtained when azochloramid was used in conjunction with sulfanilamide.

"3. The combined use of azochloramid and sulfanilamide, sulfapyridine, sulfathiazol or sulfadiazine resulted in greater inhibition of growth of pneumococcus type I than did that of either drug alone in like or somewhat higher concentrations.

"4. The combined use of sulfathiazol or sulfadiazine and azochloramid retarded the growth of *staphylococcus aureus hemolyticus* to a greater extent than did either drug in like or higher concentrations."

PILCHER, Cleveland.

Metabolism; Infant Feeding; Milk and Other Foods

INTRAVENOUS NOURISHMENT WITH PROTEIN, CARBOHYDRATE AND FAT IN MAN. DWIGHT E. CLARK and ALEXANDER BRUNSCHWIG, Proc. Soc. Exper. Biol. & Med. **49**:329 (March) 1942.

A man with extensive carcinoma of the larynx was maintained for a period of seventeen days exclusively by intravenous feedings of a mixture containing 2 parts of a 10 per cent casein digest (amigen), 1 part of a 5 or 10 per cent solution of dextrose in water or isotonic solution of sodium chloride and 1 part of fat emulsion (500 cc. of olive oil and 250 Gm. of commercial egg lecithin in 4,500 cc. of triple-distilled water). Positive nitrogen balance was maintained; plasma protein levels remained the same, and the patient maintained his weight. The authors believe this is the first recorded instance of nutrition in man by the simultaneous administration of the three primary types of foodstuffs.

HANSEN, Minneapolis.

CHRONIC DEFICIENCY OF (1) CALCIUM, (2) VITAMIN C AND (3) BOTH CALCIUM AND VITAMIN C IN MONKEYS. H. F. FRASER, Pub. Health Rep. **57**:959 (June 26) 1942.

Symptoms of calcium depletion appear after about one year on a diet containing 10.2 mg. of calcium per hundred grams of diet. These are loss of weight, weakness, muscular atrophy, irritability, decreased activity and paralysis of the legs. The bones show low calcium content. The symptoms of chronic vitamin C depletion in monkeys are anorexia, loss of weight, loss of hair, hemorrhage of the gingiva and other tissues, hemorrhages in joints and finally anky-

losis. There was no evidence that a chronic deficiency of both calcium and vitamin C influenced the course of these animals other than might be anticipated from a combination of the effects of the individual deficiencies.

SANFORD, Chicago.

MOUTH LESIONS IN MONKEYS ASSOCIATED WITH A CHRONIC DEFICIENCY OF (1) CALCIUM, (2) VITAMIN C, AND (3) BOTH CALCIUM AND VITAMIN C. H. F. FRASER, Pub. Health Rep. **57**:968 (June 26) 1942.

Monkeys (Macacus rhesus) maintained for eleven months on natural or processed foods showed little or no evidence of gingivitis. Monkeys whose store of vitamin C or of both vitamin C and calcium were chronically depleted acquired extensive lesions of the gingival and peridontal tissues. If this lesion proceeded only to the stage of inflammation and hemorrhage into the gingiva, vitamin C therapy caused a prompt arrest of the symptoms and restoration of the tissues to normal. A continuation of the condition to the stage of necrosis of the gingiva induced many lesions that did not respond to vitamin C therapy.

There was no evidence that a combination of chronic calcium deficiency and a depletion of vitamin C provoked any oral symptoms which could not have been caused by deprivation of vitamin C alone.

SANFORD, Chicago.

MILK IN NATIONAL HEALTH. E. B. HART, Wisconsin M. J. **41**:402 (May) 1942.

Milk is the best possible single food. College students have lived in good condition for six months on it, with only copper, manganese and iron added.

It cannot be said that milk contains every needed food element, for it is lacking in copper, iron, manganese and vitamin D, but otherwise it qualifies.

"All the vitamins are present in milk in adequate quantities except vitamin D, and this can be added by several well-known practical methods. The content of B-Complex vitamins is fairly abundant and also constant, due to the synthesis of these substances in the rumen of the cow."

JANNEY, Wauwatosa, Wis.

THE CALCIUM AND PHOSPHORUS CONTENT OF MILK FROM AUSTRALIAN WOMEN. B. V. RITCHIE, M. J. Australia **1**:331 (March 21) 1942.

The calcium and phosphorus content of the breast milk of 165 Australian women was found to range from 17 to 42 mg. and from 7 to 21 mg. per hundred cubic centimeters, respectively. The mean values varied according to the period of lactation. Calcium values reached their peak between the second and the fourth month and then steadily declined until the tenth month. Phosphorus values fell steadily from a peak at the first month until the eighth month, when they temporarily rose, and fell again after the ninth month. The calcium: phosphorus ratio was mostly constant throughout the period of lactation. The early onset of menstruation after parturition seemed to be a factor in the lowering of the calcium, but not of the phosphorus, values of the milk. The mean calcium and phosphorus content of the milk of mothers of rachitic infants was not significantly different from that of mothers of normal infants. The effect of the administration of extra calcium to the mother in raising the calcium level of the milk was studied in 5 cases and found to be noticeable only in the 2 cases in which vitamin D was administered concurrently with the calcium.

GONCE, Madison, Wis.

ELIMINATION OF SULFONAMIDE COMPOUNDS IN THE MILK. RAUL CIBILS AGUIRRE, J. R. CALCARAMI, D. AGUILAR GIRALDES and others, An. Soc. puericult. Buenos Aires **8**:1 (Jan.-March) 1942.

Although much is known of the sulfonamide compounds, their elimination in the milk has received little attention. The authors have studied 49 pregnancies in which the prospective mother was treated with a sulfonamide compound. They present the following conclusions:

Forty-nine pregnancies and 34 newborn infants were studied. In this study, only results from mothers who were receiving therapeutic doses of one of the drugs were used. The newborn infants fed at breast by their mothers showed neither symptoms nor intolerance. These drugs may be used in pregnancy with no untoward effects. Except when the milk "comes in," the concentration of the sulfonamide compounds in the milk is less than that in the blood. The elimination of sulfonamide drugs is variable, depending on the method of administration.

GIFFEN, Toledo, Ohio.

EFFECT OF UNDERNOURISHMENT ON THE EYES. L. ORTIN, Arch. Soc. oftal. hispano-am. **1**:1, 1942.

This article is based on the observation of some 500 undernourished patients with ophthalmic disease at Madrid during the Spanish civil war. In some the symptoms were purely subjective. Either there was slowly progressive or fulminating loss of vision, or words seemed abbreviated or distorted. Scotomas were present in 50 per cent; these were central in the majority, paracentral in less than 10 per cent and disseminated in a few. Depression of the field was unusual. Color perception was good. Dyschromatopsia with reversal of the usual order of color perception was noted.

Day blindness was rare, but night blindness was more frequent. The external conditions encountered were blepharitis, conjunctivitis and keratoconjunctivitis. Fundus changes were classed, in order of frequency, as hyperemic, edematous and mixed. The principal general symptoms were a considerable loss of weight, asthenia, frigidity of the extremities, painful paresthesias, loss of memory, scorbutic stomatitis, cutaneous manifestations, pellagroid petechiae and purpura.

W. ZENTMAYER [ARCH. OPHTH.].

Vitamins; Avitaminoses

NUTRITIONAL DERMATOSES IN THE RAT: VI. THE EFFECT OF PANTOTHENIC ACID DEFICIENCY. MAURICE SULLIVAN and JANE NICHOLLS, Arch. Dermat. & Syph. **45**:917 (May) 1942.

The article includes a review and discussion of the literature relative to the various factors of the vitamin B complex. The authors summarize their results as follows:

"1 When young piebald rats were fed a purified diet low in the vitamin B complex and supplemented with synthetic forms of thiamine, riboflavin, pyridoxine and nicotinic acid, growth was retarded and the following cutaneous alterations were observed: changes in the luster and texture of the fur, mild generalized scaling, small eczematous crusted plaques, diffuse alopecia of the venter and the preauricular regions, alopecia with or without inflammation in the circumocular regions, mild diffuse scaling of the paws, scaling, ridging and curling of the tails and symmetric pattern graying of the fur of the hood. Histologically there were mild hyperkeratosis, acanthosis, occasionally parakeratosis and a slight amount of edema and vesiculation. There was a characteristic dilatation of the hair follicles. In the late stage the epidermis and the cutis were of approximately normal thickness, and there was a moderate amount of subcutaneous fat. Disintegration of the sebaceous glands occurred in the late stages in the areas of alopecia.

"2. Supplementation with pantothenic acid promoted growth and prevented and cured the generalized dermatitis and the symmetric pattern grayness. It had no effect on the scaling of the paws and the ridging, curling and scaling of the tails.

"3. Liver filtrate preparations prevented or cured all the cutaneous signs observed. Corn oil prevented or cured scaly paws and the scaly, ridged curled tails but had no effect on the generalized dermatitis."

JACKSON, Iowa City.

THE INFLUENCE OF DIET ON THE ASCORBIC ACID REQUIREMENT OF PREMATURE INFANTS. MARGARET DANN, J. Clin. Investigation **21**:139 (March) 1942.

Data obtained on premature infants indicate that one of the factors determining the need for ascorbic acid is the level of protein intake. The response of the ascorbic acid level of the blood plasma to a test dose of the vitamin was used as a criterion of the degree of saturation of the tissues. Eleven infants given human milk showed values for ascorbic acid ranging from 1.3 to 3.5 mg. per hundred cubic centimeters four hours after a test dose of either 100 mg. of ascorbic acid injected intramuscularly or 200 mg. given by mouth, the average value being 1.9 mg. per hundred cubic centimeters. Eleven infants whose feedings consisted of various cow's milk formulas responded to test doses with values having a range of 0.1 to 1.6 mg. per hundred cubic centimeters, only 3 being above 1.2 mg. per hundred cubic centimeters; the average was 0.8 mg. per hundred cubic centimeters. The results are interpreted as signifying that premature infants receiving human milk retain a larger part of a "saturation" dose of ascorbic acid in their tissues than do infants given cow's milk. The hypothesis is offered that an increased daily requirement of vitamin C is related to a high level of protein intake. This explanation is in accord with available evidence that ascorbic acid is concerned in the intermediary metabolism of aromatic amino acids.

GUEST, Cincinnati.

DARK ADAPTATION OF CHILDREN IN RELATION TO DIETARY LEVELS OF VITAMIN A. HELEN OLDHAM, LYDIA J. ROBERTS, KATHRYN MACLENNAN and F. W. SCHLUTZ, J. Pediat. **20**:740 (June) 1942.

Oldham and associates extensively investigated three groups of children, analyzing their diets as to intake of vitamin A. The first group consisted of 100 children from a poor section of the city; the diets of the majority of these children were low in vitamin A. The second group was composed of 45 children from a school where the diet was adequate. The third group, of 23 children, were in excellent physical condition, and their diets contained abundant vitamin A.

Adaptometer studies were made and revealed little significant difference in the three groups; the same percentage in each group showed subnormal dark adaptation. After the first group was divided further into fifty pairs, 1 member of each receiving 25,000 U. S. P. units of vitamin A daily for nine weeks, tests were again made. A slight but significant improvement in dark adaptation occurred in the subjects receiving the vitamin.

STETTENBENZ, Buffalo.

PATHOLOGY OF ARTIFICIALLY INDUCED SCURVY IN THE MONKEY WITH OR WITHOUT CHRONIC CALCIUM DEFICIENCY. T. H. TOMLINSON, Pub. Health Rep. **57**:987 (July 3) 1942.

Recurrent induced scurvy in Rhesus monkeys caused gingivitis and hemorrhages into the periosteum, joints, muscles and skin; exophthalmos from subperiosteal hemorrhage within the orbits also occurred. A chronic calcium deficiency produced a severe osteoporosis and softening of all bones. Both together produced a pronounced softening of the bone in addition to the lesions of scurvy. However, the results suggest that such lesions may perhaps be somewhat less severe when calcium is withheld.

SANFORD, Chicago.

THE PROPHYLACTIC USE OF VITAMIN K IN OBSTETRICS. L. M. HELLMAN and L. B. SHETTLES, South. M. J. **35**:289 (March) 1942.

The author believes that a certain number of infant lives can be saved by the administration of as little as 2 mg. of menadione (2-methyl-1,4-naphthoquinone) to mothers during labor.

While this method of therapy is adequate, consideration of the study of the effect of such treatment on retinal hemorrhage would seem to indicate that more prolonged therapy prior to the onset of labor ought to be more satisfactory.

The author recommends that mothers should receive 2 mg. of menadione or a similarly potent vitamin K–active substance every day for at least two weeks prior to the onset of labor.

SCHLUTZ, Chicago.

THE RELATIVE NEEDS OF YOUNG MALE AND FEMALE RATS FOR VITAMIN A. KATHERINE H. COWARD, Brit. M. J. **1**:435 (April 4) 1942.

From experiments on a large series of male and female rats it was found that after the vitamin A reserve had been depleted the gain in weight was relatively greater in females than in males when small doses of vitamin A were given. When larger doses were given, the gain was equal in the males and the females. When large doses were given, it was found that the gain was greater in the males. The percentage of deaths among male and female rats whose dietary supply of vitamin A had been restricted was calculated. It was shown that a larger percentage of male rats died than of female. For this reason it is concluded that males are more susceptible to a vitamin A deficiency than are females. The cause for this is not stated. There are a few charts in this article which present the various statistical data of these experiments.

BIRDSONG, University, Va.

INTRADERMAL TEST FOR VITAMIN C IN A CASE OF SCURVY. P. B. SASTRY and D. V. S. REDDY, J. Indian M. A. **11**:157 (March) 1942.

The authors describe a case of scurvy in which Rotter's test (intradermal injection of a solution of 2,6-dichlorophenolindophenol) showed a decolorization time of only fourteen and one-half minutes instead of an expected much longer time. However, during treatment a gradual and pronounced decrease in the test time was synchronous with the clinical improvement and was only four minutes when recovery was complete.

GONCE JR., Madison, Wis.

RICKETS IN INFANTS AGED UNDER ONE YEAR: THE INCIDENCE IN AN AUSTRALIAN COMMUNITY AND A CONSIDERATION OF THE ETIOLOGICAL FACTORS. F. W. CLEMENTS, M. J. Australia **1**:336 (March 21) 1942.

Out of 500 infants observed during the last two and a half years about 50 per cent had mild rickets at some time during the first year of life. In a high percentage of the cases studied the diagnosis could be made only by roentgen examination of the growing end of a long bone, for in these cases the classic clinical features of rickets did not develop. When the rickets persisted for more than three months some of the classic clinical signs appeared, particularly epiphysial enlargement and hyperplasia of the costochondral junctions. The disturbed calcium metabolism appeared to have some effect on the rate of growth, which was slowed down. An increase in the soft tissues, which became soft and flabby, was characteristic in these cases. Indirect evidence is brought forward to support the suggestion that the fetal skeleton acts as a reservoir for the calcium required during the early months of life. While a certain basic quantity of calcium necessary to lay the foundation of the fetal skeleton may in the complete absence of calcium from the diet be withdrawn from the maternal skeleton, extra calcium for storage in the fetal skeleton is apparently supplied from that present in the mother's food. The storage of calcium by the fetus seems to determine the immediate postnatal ossification mechanism of the infant. A maternal diet rich in calcium and vitamin D during pregnancy seems to protect the infant from rickets during the first half of the year. Poor calcium and poor vitamin D intakes by the mother, especially the former, are associated in a high percentage of cases in which rickets develops early in the infant's postnatal life. That this is not the whole story of the causation of rickets is demonstrated by the fact that only 50 per cent of the infants born of the women who consumed small quantities of milk had rickets. Postnatal feeding of the infant and even of the mother influences the development of the disease. The percentage absorption of calcium rather than the actual calcium intake (except where very low) is probably the most important factor in both the development and the persistence of rickets during the first half of the first year of life. Efficient administration of vitamin D to the infant in some form (at least 400 international units per day), commencing early in the first month of life, will assure that a high percentage of the infants will not acquire rickets. Should rickets develop, the vitamin D brings about a cure within a few months in almost all cases. The vitamin D produces these results by ensuring adequate absorption of calcium from the alimentary canal. It is doubtful whether the requisite amount of vitamin D can be developed in the body of the infant by regular exposure to the sun, and it seems that the only satisfactory method of insuring that the vitamin shall be available is its administration in some form by mouth. Limited research in Australia supported by much more extensive work overseas suggests that the optimal intake of vitamin D is about 400 international units per day.

GONCE, Madison, Wis.

Hygiene; Growth and Nutrition; Public Health

THE SOCIAL MATURITY OF THE VISUALLY HANDICAPPED PRESCHOOL CHILD. KATHRYN MAXFIELD and HARRIETT A. FJELD, Child Development **13**:335 (March) 1942.

"The chief purpose of this study was to further the development of an adequate scale for measuring the general social competence of visually handicapped preschool children. An attempt was made to ferret out specific types of behavior in which these children tend to be retarded. The first 77 items of the Vineland Social Maturity Scale, including years from zero through ten, were used as the basis for the study. An intensive study was made of the scores of 101 visually handicapped children ranging in age from nine months to six years and ten months. Tentative age norms for the visually handicapped children were obtained for 32 items, as many as possible with the existing data. The validity of the scale was checked against the case histories of 17 visually handicapped preschool children for each of whom a series of Social Maturity recordings had been obtained and for whom there were behavior notes and records of physical conditions and emotional factors. An evaluation of individual items was made on the basis of all available material and finally a tentative series of 87 items was suggested as the basis for a new study. Twenty of these were taken from the Vineland Social Maturity Scale without revision, thirty-one with revision; thirty-six were new items taken from various sources and from the experience of the investigators with visually handicapped children."

AUTHORS' ABSTRACT.

A Study of Height in White School Children from 1937 to 1940 and a Comparison of Different Height-Weight Indices. Georg Wolff, Child Development **13**:65, (March) 1942.

"The present study is the third of a series dealing with the pattern of growth in white school children of Hagerstown. The material reports on nearly 20,000 height measurements during four successive calendar years. While the former ones showed a consistent upward trend in body weight, mean stature of the same children, 6 to 16 years of age, has been fairly constant in the period under observation. The behavior of the sex difference is very much alike for height as it is for weight during the growing years. There is only one minor deviation in the prepuberty stage of the sexes insofar as the female curve crosses the male somewhat earlier for stature than for weight. The nearly uniform trend of the sex differences makes it obvious that it is not so much the sex but the stature that determines the weight of a growing person. The variability of stature shows a slight upward trend with age and decreases slowly after puberty; the variability of body weight is in every age group considerably greater than of stature. However, the sex difference in the variability of height and weight exhibits a similar trend and parallels up to puberty very much the sex difference in the pattern of growth itself. Three different weight-stature ratios are computed (Quetelet, Davenport-Kaup, Rohrer-Livi). They all show a certain secular tendency to increase for children of the same ages due to the increase of body weight. But neither of them remains constant over the period of normal growth; Quetelet's and Kaup's indices increase while the index ponderalis (Rohrer-Livi) decreases somewhat from 6 years of age through 16 years of age for the average child. Therefore, they cannot be used for comparing children without considering age and stature. Due to the recently demonstrated increase of average weight per unit of stature, new height-weight-age tables should be constructed."

Author's Summary.

Studies on Microorganism in Simulated Room Environments: VII. Further Observations on the Survival Rates of Streptococci and Pneumococci in Daylight and Darkness. Mathilde Solowey, Morris Solotorovsky and Leon Buchbinder, J. Bact. **43**:545 (May) 1942.

This paper reports a study of the effect of daylight on strains of group A beta hemolytic streptococci and on several strains of pneumococci; the study was undertaken in order to obtain comparative data on strains of pathogenic cocci and to inquire into the possibility that because of unusual resistance to the deleterious effects of room environment only certain strains of the bacteria are capable of epidemic spread. It was found that no significant differences in susceptibility to daylight, exist between epidemic and nonepidemic strains of group A beta hemolytic streptococci. This finding fails to support a suggestion of Keogh that ability to resist the destructive effects of room environment may be a distinguishing feature of epidemic strains. Pneumococci, although more quickly destroyed by light because of their shorter chains than are beta hemolytic streptococci, may nevertheless be susceptible to airborne transmission. The whole study should lead to further investigation.

Stoesser, Minneapolis.

Child Health in Holland, England and Scotland: Sixty Years of Progress. Charles McNeil, Brit. M. J. **1**:429 (April 4) 1942.

This is a discussion article with a few charts demonstrating the relative infant death rate in Holland, England and Scotland. The question of the discussion is why the death rate in Holland, which at the beginning of the period was extremely high, has dropped in the last sixty years, to the lowest death rate of any of the countries. England, which started sixty years ago with a better infant death rate, has not been able to keep abreast with the improvement in the rate of Holland. The various systems are discussed in detail which are too detailed to lend themselves to abstracting. In general it is recommended that more time be spent in the medical schools in teaching principles of preventive medicine and infant and child welfare. This should also include more specialized training for visiting nurses, pediatricians and public health physicians. To get the full value from this article it should be read in detail.

Birdsong, University, Va.

Prematurity and Congenital Deformities

AGNOGENIC CONGENITAL CLUBBING OF THE FINGERS AND TOES. H. B. THOMAS, Am. J. M. Sc. **203**:241 (Feb.) 1942.

The author reports a case of clubbing of the digits of unknown cause—probably congenital and familial.

This instance represents a borderline situation between acropachy and chronic osteoarthropathy.

HENSKE, Omaha.

ROENTGENOGRAPHIC STUDY OF CRANIOFACIAL DYSOSTOSIS. MANUAL ARCE and FRANCISCO ARCE, Am. J. Roentgenol. **47**:275 (Feb.) 1942.

Modifications of development of the skull as a group are due to pathologic dysostosis or synostotis in the vault causing anomalous development of certain regions of the skull. According to the theory of Isola, the modifications are due to the fact that the skull with pathologic synostosis of a suture develops very little in the direction perpendicular to the affected suture, but in an exaggerated way parallel to it.

Types of skull are discussed according to Isola's classification: trigonocephalic, scaphocephalic, plagiocephalic, platycephalic, acrocephalic and oscephalic. A nonhereditary, nonfamilial group of dysostoses are included, with differential points.

The etiologic factors of this last group are included in some of the following: infectious, traumatic, syphilitic, changes in fetal membrane and fetal hyperthyroidism. Eight cases of cranial and craniofacial dysostoses are presented with roentgenograms. Differentiation between the conditions presented in these cases and those of true Crouzen's disease is given.

Diagnosis is based chiefly on careful study of the sutures to differentiate dehiscence of normal sutures due to increased intracranial pressure and pathologic synostosis.

SQUIRE, Chicago.

CONGENITAL FORWARD SHOULDERS (QUADRUPEDAL TYPE): TREATMENT BY CLAVICULAR OSTEOTOMY. J. E. MILGRAM, Bull. Hosp. Joint Dis. **3**:93 (July) 1942.

A case of quadrupedal type of scapulas is presented. The position of both shoulder girdles was corrected by simple clavicular wedge osteotomy in the outer thirds. The scapulas could be rotated from the sagittal to the frontal plane without difficulty.

AUTHOR'S SUMMARY.

THE ACID-BASE BALANCE OF PREMATURE INFANTS. W. STERRY BRANNING, J. Clin. Investigation **21**:101 (Jan.) 1942.

Studies of the acid-base balance of the blood of 17 premature infants led to the following conclusions: The plasma content of organic acids of premature infants is two to three times as great as that of full term infants and of adults. Ketone bodies are not responsible for this excess of organic acids. Premature infants excrete two to five times as much organic acid per kilogram of body weight per day as normal adults. Although the electrolyte pattern in the plasma differs greatly from that of the term infant, it is fairly rigidly maintained and is not appreciably altered by alkali therapy. The organic acid and carbon dioxide contents of plasma of clinically acidotic (hyperpneic) premature infants differ little from those of infants who are clinically thriving. This is taken to indicate that the premature infant is always on the borderlne of acidosis.

GUEST, Cincinnati.

SOME OBSERVATIONS ON EARLY HUMAN FETAL MOVEMENTS. JAMES E. FITZGERALD and WILLIAM F. WINDLE, J. Comp. Neurol. **76**:159 (Feb.) 1942.

Fitzgerald and Windle studied 15 human fetuses between 7 and 9 weeks of gestation (18 to 26 mm. crown-rump length) under various operating conditions. Regardless of the type or strength of stimuli used, no fetal movements of a reflex nature could be elicited from the 6 specimens during general anesthesia, after preoperative administration of morphine or after injection of solution of posterior pituitary U. S. P., or from the 6 fetuses delivered after procaine anesthesia preceded by use of morphine or solution of posterior pituitary. Three specimens observed at operations performed with the mother under spinal anesthesia and with no preoperative medication reacted to appropriate stimulation. Continuous motion picture records of the experiments were made. The estimated age of the responding fetuses was 54 to 58

days (22.5 to 26 mm. crown-rump length). The responses were of two types. While the fetus was receiving oxygenated blood the excitability was high. After anoxia had set in a lateral movement of the head and trunk followed stimulation of the parts of the face supplied by the fifth nerve. The fetal muscles retained excitability long after all reflexes had disappeared. ADDISON, Philadelphia [ARCH. NEUROL. & PSYCHIAT.].

THE CARE OF PREMATURES IN A SMALL HOSPITAL. J. L. BLANTON, South. M. J. **35**:293 (March) 1942.

The author shows the trend of premature mortality in a small hospital where the simple principles of supervision of premature infants have been established.

The equipment needed is inexpensive. A trained nursing personnel under competent supervision is essential.

Small hospitals scattered all over the country should be an integral part of the national program for supervision of premature infants. Improved care of premature infants will lead to improved nursery care of the newborn, and this will still further reduce the neonatal mortality. SCHLUTZ, Chicago.

THE CLINICAL HISTORY OF A FAMILY OF MIDGETS. C. TORRES UMAÑA, Rev. colomb. de pediat. y puericult. **1**:107 (Feb.) 1942.

A pair of syphilitic but otherwise apparently normal persons, each of whom had previously had normal offspring by other mates, became the parents of 6 children; of these 4 were midgets. In each of the cases the history was elicited that the child had been in all respects normal at birth and that physical peculiarities first made their appearance at about 15 months of age. At the time of examination the ages of the children varied from 9 months to 13 years 9 months and their heights from 67 to 77 cm. There were 2 boys and 2 girls. The characteristic features were unusual smoothness and hyperpigmentation of the skin, macroglossia, depression of the nasion, short, stubby hands, hypoplasia of the nails of the fingers and toes, genu recurvatum, poorly developed teeth, hoarse voice and varying enlargement of the liver and spleen. Three showed mental defect. The dwarfism is described as proportionate; this is not borne out by the published photographs, which suggest the presence of chondrodystrophic disproportion between the extremities and trunk. Three of the 4 gave positive serologic reactions for syphilis. In 2 cases the rate of basal metabolism was insignificantly elevated; in 2 cases the blood cholesterol was normal. Roentgen examination showed features of atypical achondroplasia—although not so interpreted by the author. Autopsy on 1 patient who died of measles complicated with pneumonia revealed fibrosis of the thymus and testes with minor changes in the hypophysis and the thyroid gland. Although the possibility of a genetic basis for the syndrome is referred to, the hypothesis is submitted that it is due to the syphilitic disease of the hypophysis. McCUNE, New York.

Acute Contagious Diseases

PLASMA AMINO-ACID LEVELS IN HEALTH AND IN MEASLES, SCARLET FEVER AND PNEUMONIA. LEE E. FARR, WILLIAM C. McCARTHY and THOMAS FRANCIS JR., Am. J. M. Sc. **203**:668 (May) 1942.

Thirty-one determinations of the plasma amino acid concentration of 30 normal, apparently healthy persons averaged 4.50 mg. per hundred cubic centimeters by the ninhydrin-carbon dioxide method. The standard deviation was ± 0.46 and the observed range 3.75 to 5.56 mg. per hundred cubic centimeters.

In patients with scarlet fever and measles, the plasma concentration of amino acid nitrogen was found to be low at the time of onset. With recovery from pneumonia the concentration returned to the normal range. Patients admitted to the hospital after the fourth day of disease failed to show significantly low levels of amino acids.

In patients with scarlet fever and measles, the plasma concentration of amino acid nitrogen was usually within the normal range. However, because of the difficulty of ascertaining the time of onset of these diseases, the data do not exclude the possibility of a deficiency of amino acids in the plasma during the preeruptive phase of these diseases. HENSKE, Nebraska.

MENINGOCOCCAL MENINGITIS. EUGENE P. CAMPBELL, Ann. Int. Med. **16**:694 (April) 1942.

Fifty cases of meningococcic meningitis are reported. Forty of the patients were treated with serum alone and 10 with serum and sulfanilamide. In the group of 40 patients treated

with serum alone, 10 deaths occurred. Among the 10 patients treated with serum and sulfanilamide no deaths occurred. The author recommends a combination of serum and sulfanilamide in the treatment of meningococcic meningitis.

READING, Galveston, Texas.

AN ANALYSIS OF FORTY-NINE CASES OF ACUTE ANTERIOR POLIOMYELITIS. G. BRUCE LEMMON JR., Pennsylvania M. J. **45**:1039, 1942.

The cases reported by Lemmon were observed during the epidemic of 1941. All the patients were hospitalized, but it is pointed out that in the presence of an epidemic persons with suspected as well as obvious cases of the disease are usually sent to a hospital. Hence the group is regarded as being fairly representative of the epidemic as a whole.

The course of the disease differed in two important respects from that usually observed in epidemics. 1. Whereas paralysis has been reported to occur in 25 to 35 per cent of patients as a rule, only 27 per cent of the present series showed complete freedom from paralysis. 2. Signs of bulbar involvement were uncommonly frequent, the incidence being 34 per cent as compared with the usual incidence of between 6 to 26 per cent.

DRAYER, Philadelphia [ARCH. NEUROL. & PSYCHIAT.].

DETECTION OF ANTIBODY BY COMPLEMENT-FIXATION IN SERA OF MAN AND MONKEY CONVALESCENT FROM MUMPS. JOHN F. ENDERS and SIDNEY COHEN, Proc. Soc. Exper. Biol. & Med. **50**:180 (May) 1942.

Saliva from a patient with mumps was injected into Stensen's duct of a monkey, after which swelling of the parotid gland appeared. The gland was excised, extracted and injected into a series of 5 monkeys with the production of similar swellings of the parotid gland. Antigens for use in the complement fixation tests were prepared by grinding with sand the gland which was removed at the height of the disease. Serums obtained from animals before the disease was induced showed no ability to fix complement; however, the serums from 6 monkeys during various periods of convalescence have shown various capacities to fix complement. Experiments with human subjects indicate that the complement-fixing antibody may appear early in some and in others be delayed.

HANSEN, Minneapolis.

STATE DIPHTHERIA IMMUNIZATION REQUIREMENTS. WILLIAM FOWLER, Pub. Health Rep. **57**:325 (March 6) 1942.

In the forty-eight states and Alaska, the District of Columbia and the territories of Hawaii and Puerto Rico only nine states require immunization against diphtheria. In five of these, New Jersey, North Carolina, North Dakota, West Virginia and Virginia, and in Alaska the provisions are statutory, while in the other four states, Illinois, Kansas, Kentucky and New York, they are found in the regulations of the state departments of health.

SANFORD, Chicago.

SULFADIAZINE IN MURINE PERTUSSIS. JOHN W. HORNIBROOK, Pub. Health Rep. **57**:535 (April 10) 1942.

When sulfadiazine was given to 20 mice one hour before they were inoculated with Haemophilus pertussis, cultures from 19 were negative while cultures from 10 of 14 controls were positive. If the drug was given three days after inoculation and the mice were killed on the seventh day after inoculation, there was no reduction in the number of positive cultures; of the cultures made on the ninth day only one in ten was positive, while all ten of the cultures from the control animals were positive.

Sulfaguanidine and sulfathiazole were less effective, and sulfanilamide was ineffective. The author concludes, therefore, that sulfadiazine reduces the number of H. pertussis organisms recoverable on culture from the lungs of mice.

SANFORD, Chicago.

PREVALENCE OF POLIOMYELITIS IN THE UNITED STATES IN 1941. C. C. DAUER, Pub. Health Rep. **57**:710 (May 8) 1942.

There were 8,947 provisional cases of poliomyelitis in the United States in 1941, with a rate of 6.8 per hundred thousand. This is 9 per cent less then 1940. An interesting map of the United States is shown, with the case frequency by counties marked. The highest incidence was in the East South Central states and the South Atlantic states. In order of frequency the figures for the states were (per hundred thousand): Alabama, 30.5; Georgia, 23.5; Tennessee, 18.4; Florida, 14.4, and Maryland, 13.1.

SANFORD, Chicago.

OBSERVATIONS DURING A RECENT EPIDEMIC OF MUMPS IN MONTREAL. R. LEVESQUE, Union méd. du Canada **71**:360 (April) 1942.

The author cites examples of atypical mumps and its complications which might well be wrongly diagnosed except during a definite epidemic. Two cases of meningitis complicating mumps and 2 cases of mumps complicated with pancreatitis are described.

About 15 cases of sublingual or submaxillary mumps were observed during the epidemic. Causes, symptoms, complications and treatment are discussed. DAFFINEE, Boston.

SOME EFFECTS OF WAR CONDITIONS ON THE 1940-41 MEASLES EPIDEMIC. ROBERT SWYER, Brit. J. Child. Dis. **39**:33 (April-June) 1942.

The author discusses the effects of evacuation, shelter life and general nutrition on the incidence and subsequent course of measles in the 1940-1941 epidemic in London.

The main features noted were: (1) the mildness of the epidemic; (2) the low incidence of important complications; (3) the unusually low case fatality rate (0.92 per cent); (4) the increased prevalence of pediculosis, scabies, impetigo and Sonne dysentery, and (5) the small number of postadmission cross infections.

A series of 1,193 cases is described and compared with a similar series of 1,603 cases from the 1933-1934 epidemic and 1,322 cases from 1935-1936 epidemic. LANGMANN, New York.

APPLICATION OF HIRST'S PHENOMENON TO THE TITRATION OF VACCINIA VIRUS AND VACCINIA IMMUNE SERUM. F. P. O. NAGLER, M. J. Australia **1**:281 (March 7) 1942.

In July 1941 Hirst described the phenomenon of agglutination of red cells by allantoic fluid of chick embryos infected with influenza virus. The author confirmed this work and then applied similar methods to vaccinia virus, which he found to have a similar effect on the red blood cells of the fowl. He described in detail his method of growing the virus on the chorioallantoic membrane of ten day chick embryos and then concentrating it to such an extent that agglutination with the red blood cells of hens was produced with a dilution of 1:256. Antibodies in rabbit and human serum following vaccination were then demonstrated and quantitatively estimated by virus-neutralizing potencies.

These experiments offer a more available and sensitive test than the mouse intracerebral method, which had hitherto been the only satisfactory means of estimating the immunologic response to vaccination other than revaccination at various times afterward. The use of the agglutination test also provides a rapid determination of the potency of materials prepared for vaccination. FRUMESS, Denver [ARCH. DERMAT. & SYPH.].

MUMPS MENINGO-ENCEPHALITIS. P. W. GILL, M. J. Australia **1**:439 (April 11) 1942.

Two cases of meningoencephalitis complicating mumps are reported. In one there was a history of contact with mumps but neither parotitis nor orchitis appeared; in the other, parotitis appeared on the fifth day of the encephalitis. GONCE JR., Madison, Wis.

MALIGNANT DIPHTHERIA (NASAL-BUCCAL-PHARYNGEAL-LINGUAL). M. E. MANTERO, M. E. IGLESIAS and B. RODRIGUEZ ABADIE, Arch. de pediat. d. Uruguay **13**:102 (Feb.) 1942.

The authors report this condition in an infant 3 years old who was operated on while under general anesthesia for a hydatid cyst of the right kidney. The child had an acute coryza, probably due to unrecognized diphtheria at the time of the operation.

Three days after the operation fever developed, and very rapidly manifestations of diphtheria appeared successively on the lips, tongue and larynx. In all the lesions the diphtheria bacillus was found. The condition rapidly grew worse, and the child died within a short time after operation.

The authors believe that the rapid and malignant development of the disease and its localization were due to the depressant effect of the general anesthesia and the performance of the operation, which lowered the child's resistance. SCHLUTZ, Chicago.

THERAPY OF CEREBROSPINAL MENINGITIS. CLEMENTE CARRILLÓ CARDENAS, Prensa méd. mex. **7**:52 (April 15) 1942.

Cardenas states that he does not intend to introduce any modification of the serum treatment of spinal meningitis. Four cases are reported in which the patients were cured by puncture of the cisterna magna and a puncture low in the spinal column made at the same time.

These 4 patients were much improved twenty hours after the injection: There was disappearance of muscular rigidity, absence of mental confusion and recovery of consciousness

together with descent of the temperature and clearing of the cerebrospinal fluid, a fact proved on the third day, when a puncture was made.

These patients were kept under observation for four weeks so that the results of the treatment could be observed; during this time bacterial investigations of the spinal fluid were made (found to be sterile) and at the same time the mentality of the patients was observed.

GIFFEN, Toledo, Ohio.

AN ANALYSIS OF THE ENZYMATIC EFFECT OF PEPSIN ON ANTIDIPHTHERIA SERUM. F. MODERN and G. RUFF, Rev. Soc. argent. de biol. **18**:93 (May) 1942.

The authors studied the proteins of antidiphtheritic serum after proteolysis by the technic described by Wasteneys and Borsook (1924). They also determined the optimum concentration of sodium sulfate for purification.

McCUNE, New York.

WELTMANN REACTION IN SCARLET FEVER. FRIEDERIKE BARTH, Ann. pædiat. **158**:335, 1942.

"The *Weltmann* reaction was applied in 102 cases of scarlet fever twice or more times in the course of the illness.

"The coagulation band is slightly but definitely shortened at the beginning of the illness and is normal or slightly broadened at the end of the illness.

"This change always corresponds with the blood sedimentation. No parallelism with the severity of the illness, especially scarlet fever angina, was observed." AUTHOR'S SUMMARY.

Acute Infectious Diseases

FURTHER STUDIES IN IMMUNIZATION AGAINST RHEUMATIC FEVER. V. P. WASSON and E. E. BROWN, Am. Heart J. **23**:291 (March) 1942.

The authors report further satisfactory results of immunization of children with rheumatic cardiac disease with hemolytic streptococcus filtrate. It is their observation after eight years' experience with this method that the treated patients have shown a pronounced reduction in the number of attacks of rheumatic fever and general improvement in health.

GIBSON, Chicago.

SULFADIAZINE: A STUDY OF ITS EFFECT ON HEMOLYTIC STREPTOCOCCI. CHARLES H. RAMMELKAMP and CHESTER S. KEEFER, Ann. Int. Med. **16**:659 (April) 1942.

According to recent evidence, sulfadiazine is superior to sulfanilamide in the treatment of streptococcic infections in human beings.

READING, Galveston, Texas.

SERODIAGNOSIS OF TRICHINOSIS BY MEANS OF COMPLEMENT FIXATION. ERNEST WITEBSKY, PHILIP WELS and ANNE HEIDE, New York State J. Med. **42**:431 (March 1) 1942.

The authors present methods of preparation of material for a complement fixation test for trichinosis. The test has been made on both rabbits and human beings and is reported to be sensitive and specific. It can be carried out as a quantitative procedure.

AIKMAN, Rochester, N. Y.

UNDULANT FEVER: A SMALL OUTBREAK IN A GIRLS' SCHOOL. J. C. CRUICKSHANK and G. A. STEVENSON, Brit. M. J. **1**:522 (April 25) 1942.

The purpose of this report was to put on record the occurrence of a small outbreak of undulant fever occurring in a girls' boarding school which was due to the consumption of unheated milk from a herd of cows infected with Brucella abortus. The total number of girls in this school was 64, and there was a staff of 14 teachers and maids. Four cases are reported. In 3 of the cases typical strains of bacilli were isolated from the blood. The herd of cattle from which the milk supply was obtained had been seen on a previous occasion because of the occurrence of abortion. It was thought at first that these abortions were due to a low-flying airplane; however, it was later shown that 2 of the cattle tested were infected with Br. abortus, and since that time all the herd had been inoculated with the Br. abortus vaccine. In the conclusion the authors state that this small epidemic of Brucella infection was due to the consumption of raw milk obtained from infected cattle and that epidemics can be prevented by proper examination of herds and pasteurization of milk.

BIRDSONG, University, Va.

GLANDULAR FEVER (INFECTIOUS MONONUCLEOSIS). J. TELFER SMEALL, Edinburgh M. J. **49**: 291 (May) 1942.

The author gives a useful conspectus of glandular fever, although the chief object of his paper is to discuss the Paul-Bunnell test, known in certain parts of Europe as the Hanganutziu-Deicher test, abbreviated H. A. R. (*heterophile Antikörperreaktion*). The technic of Paul and Bunnell had been previously devised by Davidsohn. The author's present series of observations of this test was made upon 765 specimens of serum of persons not known to be suffering from infectious mononucleosis or serum sickness.

The author feels that the diagnosis of glandular fever depends on the presence of three pictures which should not be separated: clinical, hematologic and serologic. Clinically however, there may not be any obvious glandular enlargement; hematologically the typical mononucleosis may not yet have developed, while the agglutination test may give negative results in as high as 10 per cent of the serums tested. The latter might show a positive reaction if tested later.

NEFF, Kansas City, Mo.

ACUTE MYELITIS (POST ANTI-RABIC INOCULATION). M. L. DANG, J. Indian M. A. **11**: 173 (March) 1942.

The author reports a case of acute myelitis with the signs of an acute transverse lesion of the cord. The symptoms appeared six days after the sixth injection of antirabic serum, and complete recovery took place in a month.

GONCE, Madison, Wis.

A CASE OF TETANUS OF SEROLOGICAL INTEREST. M. ROBINSON, M. J. Australia **1**:381 (March 28) 1942.

The author reports a case in which tetanus was acquired nine months after one injection of tetanus toxoid had been given.

GONCE, Madison, Wis.

THE TREATMENT OF EXPERIMENTAL ANTHRAX WITH SULPHAPYRIDINE (M & B 693). M. STERNE, South African M. J. **16**:121 (March 28) 1942.

The development of anthrax in guinea pigs could be inhibited if sulfapyridine was given by the mouth an hour after infection. Delayed administration, however, could modify but not cure the infection. Advanced anthrax in guinea pigs could be cured by injecting antiserum, sulfapyridine or gentian violet into the local lesion. Sulfarsphenamine had no therapeutic effect. Sulfapyridine treatment of virulent anthrax in rabbits and sheep had a limited success.

GONCE, Madison, Wis.

AN ACCOUNT OF RECENT FOOD INFECTION OUTBREAKS CAUSED BY ORGANISMS OF THE SALMONELLA GROUP INVESTIGATED AT THE SOUTH AFRICAN INSTITUTE FOR MEDICAL RESEARCH, JOHANNESBURG. J. GEAR, P. ROUX and C DE V. BEVAN, South African M. J. **16**:125 (March 28) 1942.

In three of four outbreaks of food poisoning studied it was possible to trace the infection to one foodstuff consumed at the suspected meal. The respective foods concerned were lettuce, beef and mincemeat. These outbreaks, in all of which the food poisoning was due to organisms of the Salmonella group, confirm the fact that the source of the infection is usually infected meat derived from animals suffering from Salmonella infections or foodstuffs contaminated by excreta from infected rats or mice.

GONCE, Madison, Wis.

SHOCK TREATMENT IN TYPHOID OF CHILDHOOD. E. PELUFFO and J. M. PORTILLO, Arch. de pediat. d. Uruguay **13**:257 (May) 1942.

The authors report that the shock treatment of typhoid in childhood was efficacious in 50 per cent of the cases in which it was used. The best results were obtained in cases of simple typhoid.

The most striking effect is the early reduction of the febrile period of the disease. The infant offers more resistance than the adult to the shock medication. Relatively high initial doses of vaccine in hypertonic solution of dextrose must be given. The medication is most effective if employed very early in the disease. Age does not seem to have a great influence on the effectiveness or ineffectiveness of the medication. Children with severe typhoid do not respond readily to the shock medication.

If results are not observed after the fourth or fifth injection of vaccine, favorable results cannot be expected with additional dosage. In cases of the severe forms of typhoid the medication not only is ineffective but may even prove to be harmful.

SCHLUTZ, Chicago.

ONCHOCERCIASIS AND THE EPILEPTIC SYNDROME. I. BALANZARIO, Prensa méd. mex. **7**:62 (May) 1942.

Balanzario found that of 319 patients with onchocerciasis examined, the high proportion of 9.09 per cent had epilepsy. He concluded that the epileptic syndrome often is associated with filariasis (onchocerciasis) when the nodules caused by the filaria act as tumors in the cranium. Filariasis acts as a sufficient factor in itself to produce epilepsy. GIFFEN, Toledo, Ohio.

SODOKU (A CASE OF ITS OCCURRENCE IN A GIRL OF TWO YEARS). NICOS FACATSELLI, Ann. pædiat. **158**:216, 1942.

Facatselli reports a case of typical rat bite fever; there was a scar proved to be from the bite of a rat, a pseudophlegmonous swelling of the arm, swelling of the axillary glands and fever. A positive Wassermann reaction was elicited. The disease was successfully transferred to a guinea pig by injections of the child's blood; spirilla (Spirochaeta morsus murium) were found in its blood. The child was cured by the use of sulfarsphenamine.

EDITOR'S SUMMARY.

Chronic Infectious Diseases

TUBERCULOSIS IN DERMATOLOGIC DIAGNOSIS, WITH SPECIAL REFERENCE TO THE PURIFIED PROTEIN DERIVATIVE (P. P. D.). CARMEN C. THOMAS, Arch. Dermat. & Syph. **45**:544 (March) 1942.

The author found on the basis of 109 parallel tests on 79 patients with a wide variety of dermatoses that the purified protein derivative of tuberculin, the active principle of old tuberculin, a chemical fraction of precipitated tuberculoprotein, is equal to freshly prepared dilutions of a potent old tuberculin in detecting sensitized persons. No positive reactions were obtained with this substance in persons in whom they were not also elicited with old tuberculin, and no negative reactions occurred which were not confirmed by negative reactions with old tuberculin. Purified protein derivative is therefore specific.

Parallel tests with serial dilutions of old tuberculin showed that the first test dose (0.00002 mg.) of purified protein derivative is equivalent to approximately 0.002 mg. of old tuberculin and that the second test dose (0.005 mg.) of the derivative is equivalent to approximately 1 mg. of old tuberculin.

JACKSON, Iowa City.

ARTIFICIAL FEVER THERAPY IN JUVENILE NEUROSYPHILIS. JUUL C. NIELSEN, JOHANN R. MARX and HERMAN A. DICKEL, Arch. Dermat. & Syph. **45**:688 (April) 1942.

The authors treated 5 patients suffering from juvenile neurosyphilis with artificial fever therapy, produced with the Kettering hypertherm, and with subsequent chemotherapy. One patient died during treatment; the remainder showed physical and mental improvement during an observation period of from one to three and a half years.

JACKSON, Iowa City.

THE TUBERCULIN TEST. SOL ROY ROSENTHAL, Illinois M. J. **81**:205 (March) 1942.

Rosenthal presents a review of the entire subject of tuberculin tests: sources of tuberculin, methods of administration, reactions, dilutions to be used, choice of tests and value of tuberculin tests.

BARBOUR, Peoria, Ill.

THE SOURCE OF INFECTION IN ACTINOMYCOSIS. JOHN SLACK, J. Bact. **43**:193 (Feb.) 1942.

Two theories have been brought forth regarding the source of infection in actinomycosis, the exogenous theory, which indicates that contaminated lawns of grass or grain carry the organism to man and cattle, and the endogenous theory, which implies that man can be a carrier of the organism. The author has made a thorough investigation of the latter theory. One hundred pairs of tonsils from routine tonsillectomies were examined, and in addition 100 samples of pyorrhea pus were cultured. From the 100 pairs of tonsils colonies of anaerobic actinomycetes were found in 14 per cent of the primary mixed cultures and pure cultures of these organisms were isolated from 11 per cent of the tonsils. Monilia albicans was isolated from 12 per cent of the tonsils. From 100 samples of pyorrhea pus colonies of anaerobic actinomycetes were found in 18 per cent of the primary mixed cultures and pure cultures of the organisms were isolated from 12 per cent; M. albicans was isolated from only 1 specimen. Progressive, fatal experimental actinomycosis with sulfur granules was produced in 4 rabbits and 1 guinea pig inoculated with anaerobic actinomycetes isolated from pyorrhea pus.

STOESSER, Minneapolis.

INTRAVENOUS INJECTIONS OF SOLUBLE BISMUTH COMPOUNDS: THEIR TOXICITY, AND THEIR SOJOURN IN THE BLOOD AND ORGANS. TORALD SOLLMANN and JOSEPH SEIFTER, J. Pharmacol. & Exper. Therap. **74**:134 (Feb.) 1942.

Intravenous injection of water-soluble bismuth compounds are too toxic for clinical use. The authors investigated the toxicity of three of these compounds on rabbits and dogs, giving the solution rapidly by vein, i. e. within ten to thirty minutes, and slowly by the drip method, in four to ten hours. Toxicity by either method seemed too great to promise usefulness for this procedure clinically, although the question whether the extra high concentrations of bismuth that are secured temporarily by intravenous injection add materially to the efficacy of bismuth treatment of syphilitic infections can be answered only by direct experiments. This is being investigated elsewhere.

PILCHER, Cleveland.

THE ACTION OF CERTAIN SULFONAMIDES, SULFONES AND RELATED PHOSPHORUS COMPOUNDS IN EXPERIMENTAL TUBERCULOSIS. M. I. SMITH, E. W. EMMART and B. B. WESTFALL, J. Pharmacol. & Exper. Therap. **74**:163 (Feb.) 1942.

Certain of these drugs were found to have an inhibiting action on the tubercle bacillus in culture experiments. They also were of value in the treatment of guinea pigs which had been given intraperitoneal injections of tubercle bacilli, although the doses of the drugs were too close to the toxic level for safe clinical trial at present. These experiments and those of others give promise that related drugs of this series may prove to be of clinical value in tuberculosis infections.

PILCHER, Cleveland.

THE QUANTITATIVE NATURE OF THE COACTION OF BISMUTH AND ARSENICAL COMPOUNDS IN THE THERAPY OF EXPERIMENTAL SYPHILIS. N. M. CLAUSEN, B. J. LONGLEY and A. L. TATUM, J. Pharmacol. & Exper. Therap. **74**:324 (March) 1942.

The authors investigated the use of bismuth and arsenic compounds concurrently in the treatment of rabbits with active syphilis. It was found that the use was additive and that there was no potentiation nor antagonism. When the action of two drugs administered at the same time is equal to the sum of their individual effects the response is termed simple addition. For example, if 25, 50 or 75 per cent of the minimal curative dose of an arsenical is given with 75, 50 or 25 per cent, respectively, of the minimal curative dose of a bismuth preparation and cure is obtained with each combination, simple addition has occurred. However, the cotoxicity of the two groups was less than their separate toxicities, which means that there is a greater margin of safety when the two types of drugs are used concurrently.

PILCHER, Cleveland.

SYPHILIS IN WISCONSIN. W. F. LORENZ, Wisconsin M. J. **41**:121 (Feb.) 1942.

Wisconsin has two sources of information on the incidence of syphilis in the state: (1) applications for marriage (164,732) and (2) records of military selectees (84,701).

For members of these groups between 20 and 30 years old there is an incidence of 6 to 7 per 1,000. Fifty-one per cent are males and 49 per cent females.

Presence of the disease had been unsuspected in most cases. Of the 502 syphilitic selectees, 67 (or 11 per cent) were Negroes.

The incidence for Milwaukee was 11.6 per thousand.

JANNEY, Wauwatosa, Wis.

CONGENITAL PARROT'S DISEASE. E. PELUFFO, Arch. de pediat. d. Uruguay **13**:158 (March) 1942.

The author reports a case of this rare condition in an infant born of a mother in whom syphilis was not suspected. The child was born at term, with a history of a perfectly normal birth without the least trauma. Subsequent to birth the infant showed no signs of syphilis, and the serologic reactions were negative.

At the time of birth a total flaccid paralysis of the upper part of the left arm was noticed. The picture was that of a complete obstetric paralysis of the brachial plexus. Roentgenograms showed the absence of osseous lesions due to trauma and showed the presence of an osteochondritis.

The mother showed positive reactions to Wassermann and to Kahn tests, which confirmed the diagnosis of syphilis. Antisyphilitic treatment relieved the paralytic syndrome in a short time, but the osseous lesions became more pronounced, splenomegaly developed and the Wassermann and Kahn reaction became positive. The infant made a complete recovery.

SCHLUTZ, Chicago.

A Case of Köhler's Disease. Jorg Ferreira Machado, Med. cir. pharm. **71**:1 (Feb.) 1942.

The author reports a case of Köhler's disease in a 6 year old boy. Roentgenograms of the chest showed no lesions, but the boy's reaction to a Mantoux test with a dilution of 1:1,000 was 2 plus. The treatment consisted in the administration of calcium and vitamins.

Sanford, Chicago.

Diseases of Blood, Heart and Blood Vessels and Spleen

Rheumatic Carditis in a Tropical Country. E. G. Carrillo, Am. Heart J. **23**:170 (Feb.) 1942.

The author reports 10 cases of rheumatic fever occurring in his private practice in San José, Costa Rica. He states that while rheumatic fever may occur less frequently in a tropical climate the course is likely to be severe, resulting in multiple valvular lesions which often prove fatal.

Gibson, Chicago.

Hereditary Telangiectasis. Lawrence I. Stellar, New England J. Med. **226**:336 (Feb. 26) 1942.

Hereditary telangiectasis is a pathologic condition that occurs in and is transmitted through both sexes. The characteristic lesions, small red or purplish papules, occur in the mucous membranes, especially those of the upper respiratory and gastrointestinal tracts, in the skin and in some viscera. Hemorrhage has been reported most commonly in the form of epistaxis. The amount of loss of blood tends to increase in later life.

A detailed report of a case of this disease in an adult is given. The severe anemia (hemoglobin content 8 per cent, red cell count 900,000) was overcome by transfusions, administration of iron and daily intramuscular injections of liver extract.

Gengenbach, Denver.

Rates of Hemolysis in Human Blood Stored in Dextrose Solutions and in Other Mixtures. Elmer L. DeGowin, John E. Harris and Joy Bell, Proc. Soc. Exper. Biol. & Med. **49**:481 (March) 1942.

The addition of 3 per cent dextrose solution to citrated blood (3.2 per cent sodium citrate) stored at 2 C, decreased the hemolysis of the red cells as measured by determination of the plasma hemoglobin and by hematocrit readings. Concentrations of dextrose below 3 per cent and above 10 per cent are not effective in inhibiting hemolysis. Sucrose is not as effective as dextrose. Both sodium chloride and potassium increased the rate of hemolysis. The use of a preservative mixture containing 3 per cent dextrose permits the safe storage of blood for thirty days or more.

Hansen, Minneapolis.

Patent Interauricular Septum Associated with Mitral Stenosis: Lutembacher's Syndrome. C. J. Baylin, Radiology **38**:1 (Jan.) 1942.

Two patients were thought to have a septal defect of the auricles and stenosis of the mitral valve, the opinion being based on previous reports and on clinical roentgenologic signs. The first patient was a 15 year old boy who was said to have had heart disease at the age of 6 months. Throughout childhood he had experienced exertional dyspnea and had been unable to keep up with his playmates. The condition had been noticeably worse during the preceding four months. There was no history of rheumatism. Infections of the upper respiratory tract had been frequent. There was slight orthopnea with cyanosis on occasions. The pulse rate was 96, the respiratory rate 24 and the blood pressure 135 systolic and 90 diastolic. The lungs were clear. On roentgen examination the heart was seen to be enlarged, with prominence of the pulmonic conus; both auricles were slightly enlarged.

The second patient, a 34 year old woman, presented a somewhat similar early history but had complained of cough and hoarseness for four years. She had had polyarthritis at the age of 21 years. Increasing frequency of periods when bright red blood was coughed up led to increased dyspnea and cyanosis. Slight clubbing of the fingers was observed. The roentgen appearance was similar to that in the preceding case but differed in degree.

The syndrome described is characterized by a typical roentgenogram. The cardiac silhouette is enlarged to the right and to the left, with prominence of the pulmonary conus. The aortic shadow is usually normal or smaller than normal. There is prominence of the

hilar shadows, which are so striking that they often resemble irregular masses of lymph nodes. The border of the left auricle may be obscured by the bulging, dilated conus but is often seen enlarged to the left.

Fluoroscopic examination and roentgenograms taken in the oblique projection will serve to clarify the changes observed in the conventional roentgenogram of the chest, and the anatomic relationship of the shadows can usually be readily established.

ANSPACH, Chicago.

DISTURBANCES IN THE COAGULATION OF THE BLOOD. L. J. WITTS, Glasgow M. J. **19**:57 (March) 1942.

The author presents the accepted methods of explanation for blood clotting and gives a partial account of the development of vitamin K, heparin and coumarin. Coumarin is the substance isolated from poorly cured sweet clover which tends to lower the prothrombin level in the blood of cattle. It is also effective in human beings but has a latent period of three to four days. Heparin works more quickly. The author has also used various coagulants in the investigation of blood clotting. Russell viper serum is very active. Russell viper serum may be combined with milk, tissue extract or lecithin to provide a double-acting thromboplastin, which in the viper serum is water soluble and in the lecithin is fat soluble. A comparison of the water-soluble fraction along with that in the combined substances throws added light on the clotting mechanism of the blood. He believes this is better for investigation on human subjects than the rabbits' brain extract. He also has found that human brain extract is better than that from rabbits' brain. He feels that investigation in time will reveal something that will be effective in the treatment and care of persons with hemophilia.

SNELLING, Toronto, Canada.

HYPOPROTHROMBINEMIA PRODUCED BY METHYLENE-BIS-(HYDROXYCOUMARIN). JÖRGEN LEHMANN, Lancet **1**:318 (March 14) 1942.

Extensive experiments conducted on rabbits at the Central Laboratory, Sahlgrenska Hospital, Göteborg, Sweden, showed that methylene-bis-(hydroxycoumarin), here called antiprothrombin, produced a reproducible and reversible hypoprothrombinemia. No toxic effects could be observed on circulation, respiration, intestines, liver or kidneys. This substance should have useful application in clinical conditions in which it is desirable to depress the coagulability of the blood in vivo.

LANGMANN, New York.

ON THE VALUE OF RETROGRADE AORTOGRAPHY FOR THE DIAGNOSIS OF COARCTATION OF THE AORTA. AGUSTIN CASTELLANOS, RAÚL PEREIRAS and DAVID CAZANAS, Arch. de med. inf. **9**:9 (Jan.-March) 1942.

Four aortographs and one angiocardiograph are shown of a 6 month child with slight cyanosis, slight systolic murmur and slight enlargement of the liver. The telecardiogram showed only modifications of the cardiac shadow, while the angiocardiogram showed interauricular and interventricular communication with a total transposition of the large vessels and the aorta lodged to the right. The retrograde aortograph showed that besides these conditions there was also an aortic coarctation. The authors state that for the first time in the history of cardiography and roentgenography they are able to obtain a roentgenogram of the heart and large vessels by the injection of contrast substances from the peripheral vessels (humerals).

SANFORD, Chicago.

HEMORRHAGIC PURPURA DUE TO TOXIC EFFECTS OF QUININE SALTS. R. P. VARAS, Bol. Soc. cubana de pediat. **14**:49 (Feb.) 1942.

The author reports a case of hemorrhagic purpura in a white child aged 4 years. The child had been treated with quinine salts for a febrile condition on the suspicion that the elevation of temperature was due to a malarial condition. Shortly after the use of this remedy hemorrhagic manifestations in the form of purpuric spots appeared on the inferior extremities and extended to the trunk and face. There was also gingival bleeding.

The author ascribes the appearance of purpuric manifestations to the toxic effect of the quinine salts. The use of liver extract, vitamin K and calcium chloride by mouth, with suitable dietary measures, completely restored the child within a short time.

SCHLUTZ, Chicago.

Diseases of Nose, Throat and Ear

CONGENITAL AURAL FISTULA. MEYER S. FOX, Arch. Otolaryng. **35**:431 (March) 1942.

Six cases of aural fistula, unusual because of their occurrence in one family, demonstrating clearly the familial and hereditary features of the involvement, are presented.

GREENWOOD, Chicago.

SULFANILAMIDE IN OTITIS MEDIA IN CHILDREN: FURTHER REPORT ON A CONTROLLED SERIES. EDWIN B. BILCHICK and GEORGE HUNTER O'KANE, Laryngoscope **52**:341 (May) 1942.

Bilchick and O'Kane compare the results in their two controlled series of children with otitis media who were treated with sulfanilamide or a derivative. The first 103 patients were treated during January, February and March 1939, 55 being given sulfanilamide and 48 being used as controls, without any sulfonamide drugs. During the winter months of 1940, under the same conditions as those observed the year before, 80 patients were studied, one-half receiving a sulfonamide drug and the others none. A different dose of the drug was used in the two series. In 1939 moderate doses were employed, while in 1940 larger doses were given earlier in the disease. In the 1940 series, 200 mg. of sulfanilamide or an allied compound per kilogram of body weight was given in divided doses during the first twenty-four hours, followed by a daily amount of 120 mg. per kilogram. Sodium bicarbonate was administered with the drug. The medication was continued for from four to seven days after apparent cure. In the 1939 series, those who received moderate doses of the drug, the duration of the aural discharge for the sulfanilamide-treated patients was one-half that for the controls, but the number of mastoidectomies necessary was not affected. In the 1940 series, the use of the sulfonamide drug earlier and in larger doses reduced the duration of the disease one third and the number of mastoidectomies over one half. No serious complications resulted from the therapy. There were 5 cases of early and 3 cases of late recurrence of the otitic infection between one and six weeks after the ear was dry and use of the drug was stopped. In several of these cases repeated myringotomy was necessary. There were no relapses in the control series.

WOOD, Newark, N. J. [ARCH. OTOLARYNG.]

CONGENITAL CHOANAL OCCLUSION. W. L. BONHAM, South. M. J. **35**:252 (March) 1942.

The author believes that the existence of congenital choanal occlusion should be made known to obstetricians, pediatricians and general practitioners in order that an early diagnosis may be made and the lives of some infants saved.

The diagnosis is relatively simple if one is cognizant of the existence of such a condition and will use a probe, catheter, postnasal mirror and digital palpation of the nasopharynx. This may then be followed by roentgen examination after instillation of iodized oil into the nasal cavities. The type of surgical treatment will vary with the age of the patient.

SCHLUTZ, Chicago.

AN EVALUATION OF THE AUDIOMETER IN TESTING HEARING. C. C. SWANN, South. M. J. **35**:280 (March) 1942.

The author believes the audiogram to be the most practical method by which a patient may be watched by different otologists.

A satisfactory audiogram may be made for many patients who are unable to cooperate sufficiently for other tests, and this is especially true for children.

The audiometer is the best method for testing the higher tones, and defects here call for a careful otologic and many times a complete general examination. An audiometric study should be made on every patient who complains of defective hearing.

SCHLUTZ, Chicago.

TONSILLECTOMY IN YOUNG CHILDREN. P. PANNETON, Union méd. du Canada **71**:239 (March) 1942.

The consensus of medical opinion is that tonsillectomy should not be performed on children under 5 years of age except for extraordinary reasons. At the Crèche d'Youville 105 such operation were performed from 1935 to 1940. During that time there were 3,108 admissions to the orphanage. Four indications for the operation were considered: (1) repeated attacks of sore throat; (2) subnormal physical condition in patients in whom nothing beyond the local abnormality could be found; (3) chronic otitis media; (4) chronic coryza with tonsillar infection. Fifty-three of the children were between 2 and 3 years of age; 30 were between 1 and

2 years, and 3 were under 1 year. The average age rose during the study, the average in the first 20 cases being 18½ months, and in the last 20 cases, 34½ months.

The author points out that few grossly hypertrophied tonsils were encountered. Results were good; there were no complications. Only 52 per cent of the patients with otitis (25) were cured. The incidence of sore throats was diminished in most of the cases.

DAFFINEE, Boston.

Diseases of Lungs, Pleura and Mediastinum

PNEUMOCOCCAL CAPSULAR POLYSACCHARIDE AND ANTIBODY IN PLEURAL EXUDATES. PAUL F. DEGARA, JESSE G. M. BULLOWA and SAMUEL C. BUKANTZ, Am. J. M. Sc. **203**: 376 (March) 1942.

Forty-four specimens of pleural exudate from 27 patients suffering from lobar pneumonia were examined bacteriologically and immunologically.

Twenty-four pleural exudates from 16 patients were positive on culture and contained detectable capsular polysaccharide but no antibody. Capsular polysaccharide was found in six sterile pleural fluids from 4 patients. On one occasion the pleural culture was positive. Fourteen fluids from 9 patients were negative on culture and contained no capsular polysaccharide; in eight of these fluids (from 4 patients) antibodies could be detected.

Eight of the 27 patients died (29.7 per cent). Capsular polysaccharide was detectable in the pleural exudates of 6.

Thoracotomy after thoracentesis was performed on 11 patients (3 deaths), while thoracenteses alone were employed for the remaining 16 patients (5 deaths). More recoveries occurred in thoracotomized patients who had had bacteremia than in those given repeated thoracenteses.

Of bloods, pleural exudates and urine from 9 patients which were studied for capsular polysaccharide, it was detected in seven pleural exudates, in five urines after concentration and in the two bloods.

Pooled serum was satisfactorily used for the detection of capsular polysaccharide in pleural exudates.

For the detection of capsular polysaccharide in pleural exudates the optimal concentrations of antibody are essentially the same as those used for its detection in urine, broth and plasma.

HENSKE, Omaha.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

TWO CASES OF DOUBLE GALL BLADDER. MEYER GOLOB and JOHN L. KANTOR, Am. J. Digest. Dis. **9**:120 (April) 1942.

These double gallbladders were visualized roentgenologically by the use of ingested dye and did not appear to be involved in any pathologic process.

It should be borne in mind that a diseased gallbladder may coexist with a normal accessory gallbladder and the diseased gallbladder not be visualized.

MORRISON, Savannah, Ga.

THE TREATMENT OF ANORECTAL INFECTIONS WITH SUPPOSITORIES CONTAINING SULFANILAMIDE AND LOCAL ANESTHETIC: PRELIMINARY REPORT. HAROLD LAUFMAN and MORTIMER DIAMOND, Am. J. Digest. Dis. **9**:144 (April) 1942.

Forty-six cases of various types of nonsuppurative anorectal inflammation are the material for this study. In 31 treatment was with suppositories containing 1 per cent sulfanilamide and metycaine hydrochloride. In 9 suppositories containing 1 per cent sulfanilamide were used, and in 6, suppositories containing no medication. Proctoscopic examination was the criterion for a cure.

Of the 31 patients treated with the sulfanilamide (1 per cent) and metycaine hydrochloride suppositories, proctoscopic examination revealed a complete cure in four weeks in 16 (51.6 per cent). Partial cures were obtained in 15 patients (48.4 per cent) in four weeks, and of these 15 patients, 5 were completely cured after eight weeks' treatment. Eighty-three and nine tenths of this series (31 patients) had complete relief from symptoms within four weeks.

When 1 per cent sulfanilamide suppositories were used, relief was not obtained as quickly, but as the cryptitis subsided, the itching and other symptoms gradually disappeared.

When the control suppository was used, no relief was obtained aside from added lubrication, and proctoscopic examination revealed no change in the appearance of the mucosa.

MORRISON, Savannah, Ga.

DIAPHRAGMATIC HERNIA OF CHILDREN. STUART W. HARRINGTON, Ann. Surg. **115**:705 (April) 1942.

Diaphragmatic hernias occurring in infants and in children present many problems of diagnosis and treatment that differ greatly from those caused by similar hernias occurring among adults. One of the principal reasons for this variation is the difference in the types of diaphragmatic hernias seen in children.

The more common types are those due to embryologic structural defects of the diaphragm and those caused by congenital absence of the diaphragm. Next in frequency are esophageal hiatus and traumatic hernia.

The author discusses these various types and the surgical treatment of them.

BANTIN, Omaha.

STUDIES OF THE ACUTE DIARRHEAL DISEASES: VI. NEW PROCEDURES IN BACTERIOLOGICAL DIAGNOSIS. ALBERT V. HARDY and JAMES WATT, Pub. Health Rep. **57**:521 (April 10) 1942.

Cultures of the feces are made on the new preparation S. S. (Shigella-Salmonella) agar, which may be purchased in the open market. Materials for culture are taken by means of cotton swabs inserted in a rubber tube. All plates are picked after eighteen to twenty-four hours and examined the following morning.

SANFORD, Chicago.

STUDIES OF THE ACUTE DIARRHEAL DISEASES: VII. CARRIERS OF SHIGELLA DYSENTERIAE. JAMES WATT and ALBERT V. HARDY, Pub. Health Rep. **57**:524 (April 10) 1942.

Convalescent and passive carriers of Shigella dysenteriae are common. A large proportion of them may be identified with relative ease if persons with diarrheal disease and their contacts are promptly studied by the use of the new highly selective culture mediums, Shigella-Salmonella agar and desoxycholate-citrate medium.

SANFORD, Chicago.

STUDIES OF THE ACUTE DIARRHEAL DISEASES: VIII. SULFAGUANIDINE IN THE CONTROL OF SHIGELLA DYSENTERIAE INFECTIONS. ALBERT V. HARDY and JAMES WATT, Pub. Health Rep. **57**:529 (April 10) 1942.

A total dose of 0.3 Gm. of sulfaguanidine per kilogram of body weight per day for at least four days was used by Hardy and Watt in the treatment of Shigella dysenteriae infections. The authors considered that the results were promising and that this method of treatment deserves adequate trial.

SANFORD, Chicago.

CONGENITAL ATRESIA OF THE ESOPHAGUS. M. FUHRMAN, D. DRAGUTSKY and G. ROOK, Radiology **38**:326 (March) 1942.

The authors report 2 cases of congenital atresia of the esophagus in newborn infants. While reports of numerous cases have been published, only 2 were recorded for 12,285 deliveries in the maternity service of the Metropolitan Hospital in New York. The authors cite Vogt's classification: type 1, complete absence of the esophagus (rare); type 2, complete atresia with no tracheoesophageal fistula (rare); type 3 A, communication of the upper segment of the esophagus with the trachea (rare); type 3 B, blind termination of the upper segment and communication of the lower with the trachea or the bronchi near the level of bifurcation of the trachea (most common type); type 3 C, communication of both segments with the trachea or bronchi (rare).

In the 2 cases reported the condition was of type 3 B. The first infant regurgitated all feedings. Several attempts to feed by gavage were unsuccessful. After exploration with a soft rubber catheter and the discovery of an obstruction of the esophagus at the level of the third thoracic vertebra, a solution of barium sulfate was administered. This was immediately aspirated into the lungs, indicating an esophageal fistula. Death ensued that evening.

In the second case an opaque oil was used as the contrast medium in the exploration of the esophagus. After the roentgen examination the oil was removed from the esophageal pouch. The catheter could not be passed down the esophagus beyond the level of the bifurcation of the trachea. Gastrostomy was performed, and the patient did well for a fortnight. Then the tube became loose; and after it had been replaced, death occurred. The necropsy examination showed atresia of the esophagus with a tracheoesophageal fistula.

The authors contend that the diagnosis can best be made without the use of a liquid contrast medium. They suggest that a soft rubber catheter be introduced through a naris into the esophagus and under fluoroscopic visualization passed downward toward the stomach.

With the patient in the Trendelenburg position a small bulb syringe is attached to the proximal end of the catheter and a few cubic centimeters of air is injected. The air will clearly outline the esophageal pouch. They emphasize the fact that gas in the intestinal tract indicates the presence of a fistulous communication between the lower segment of the esophagus and the respiratory passages. ANSPACH, Chicago.

SULPHONAMIDE COMPOUNDS IN FECES. FRANK HAWKING, Lancet **1**:290 (March 7) 1942.

In the feces of normal persons sulfaguanidine was excreted in high concentrations, while sulfapyridine, sulfathiazole, sulfadiazine and sulfanilylbenzamide were found only in fairly low concentrations. These results seem to support the view that sulfaguanidine will prove particularly suitable for the treatment of bacillary dysentery. LANGMANN, New York.

A STUDY OF CHOLANGIOPATHIES IN CHILDHOOD. A. B. CESAR, Bol. Soc. cubana de pediat. **14**:113 (March) 1942.

The author points out that in obscure abdominal conditions in childhood one should not overlook disease of the biliary tract. Careful study of bile function and biliary excretion, and study by means of cholecystography have shown that these conditions are more frequent in children than has been ordinarily supposed. SCHLUTZ, Chicago.

Nervous Diseases

THE PROGNOSIS OF PNEUMOCOCCIC MENINGITIS TREATED WITH CHEMOTHERAPY. G. HOLLANDER, Am. J. M. Sc. **203**:370 (March) 1942.

The clinical results obtained in 160 reported cases of pneumococcic meningitis treated with chemotherapy bear out experimental results that sulfapyridine is the drug of choice in the treatment of this infection.

At present there is no clear evidence that the additional use of specific serum with sulfapyridine should be a routine procedure. The percentage of recovery with sulfapyridine alone is approximately that of combined sulfapyridine-serum therapy. The combination is indicated in the treatment of type III and type V pneumococcic meningitis, in the treatment of infections secondary to an otorhinologic condition and to pneumonia, and in the treatment of younger patients.

No definite correlation could be made between the dose of the sulfonamide drug used, its concentrations in both blood and spinal fluid and the clinical response.

The prognosis is favorable if the cerebrospinal fluid has been sterilized within four days with the use of sulfapyridine.

Almost every type of pneumococcus has been cultured from patients with pneumococcic meningitis. With the exception of types III and V, there is little correlation between the type of organism and the prognosis.

The prognosis in pneumococcic meningitis secondary to pneumonia is poor, possibly because of an acquired tolerance of the invading organism to the sulfonamide drug.

The prognosis in the younger age groups is improved with the use of combined drug and serum therapy, with the best prognosis occurring in the age group from 10 to 20 years.

Of 9 patients with pneumococcic meningitis treated at Jefferson Hospital with chemotherapy, only 1 recovered. Two others, infected with pneumococci of types III and X, had apparently recovered but died following unsuccessful treatment of a relapse. The patient who recovered received combined sulfapyridine and serum therapy. HENSKE, Omaha.

PARATHYROID INSUFFICIENCY IN WILSON'S DISEASE. RUDOLF ALTSCHUL and J. S. BROWN, Canad. M. A. J. **46**:237 (March) 1942.

This report deals with 4 cases of hepatolenticular degeneration occurring in a family of 5 children.

In the 2 older children there was the complicating factor of parathyroid deficiency. In the second of these 2 children postmortem examination showed atrophy of the parenchyma of the parathyroid glands and an endarteritis obliterans, which was probably the cause of the condition.

In the 3 older brothers nervous symptoms were predominant; in the youngest the symptoms were simply those of hepatic cirrhosis, although at necropsy alterations of the lenticular nuclei and their surroundings were noted. MOORE, Omaha.

STUDIES ON THE PHOSPHORUS COMPOUNDS OF BRAIN. S. E. KERR, J. Biol. Chem. **145**:641, 1942.

Dog brain frozen in situ with liquid air contains 19 mg. of acid-soluble purine nucleotide and 2 mg. of nucleoside and free purine nitrogen per hundred grams. Of the nucleotide nitrogen, 83.5 per cent is adenine. Preliminary studies indicate that the remainder is guanine, rather than hypoxanthine. The amount of acid-hydrolyzable phosphorus found attached to the nucleotide is close to that required for full phosphorylation. During autolysis loss of acid-hydrolyzable phosphorus begins within five seconds, reaching a level corresponding to adenosine diphosphate in about three minutes, after which the nucleotide nitrogen slowly decreases to half the normal level within an hour, with a corresponding increase in nucleoside and free purine. No formation of inosinic acid is observed during one hour of autolysis. Adenine, together with hypoxanthine and ribose, is found in the nucleoside-free purine fraction, the adenine decreasing during autolysis. The decomposition of nucleotide to nucleoside and free purine, with a gradual decrease of adenine in the nucleoside fraction and no increase of inosinic acid, suggests that adenylic acid in brain is first decomposed by a phosphatase, rather than by a deaminase.

PAGE, Indianapolis [ARCH. NEUROL. & PSYCHIAT.].

EXCITABILITY OF CEREBRAL CORTEX IN INFANT MACACA MULATTA. MARGARET A. KENNARD and W. S. MCCULLOCH, J. Neurophysiol. **5**:231, 1942.

Facilitation, extinction and suppression of motor response to cortical stimulation were observed in a monkey 20 days old. The movements produced were contralateral, and they were elicited only when stimuli were delivered to area 4. No responses were obtained from area 6 or from the postcentral convolution. Facilitation and extinction of motor responses were demonstrated easily. Relatively high voltages were required for successful stimulation, and responses were less prompt and discrete than in the adult. No responses could be obtained in the leg, and the hand was less easily stimulated than the face.

Lack of response from area 6 is in agreement with the fact that forced grasping is normal at this age.

Although removal of area 4-s fails to produce spasticity in monkeys of this age, stimulation of this area suppressed motor responses. Therefore, it is apparent that some mechanism other than simple release of cortical activity in area 4 must be necessary to produce the spasticity observed in older animals after the removal of area 4-s.

DRAYER, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

POSITIONAL NYSTAGMUS IN CEREBELLAR LESIONS. E. A. SPIEGEL and N. P. SCALA, J. Neurophysiol. **5**:247, 1942.

After lesions of parts of the cerebellum of cats, particularly the lobus posterior medianus, nystagmus was observed with abnormal positions of the head, particularly when the animal was in the supine position with the vertex downward. A weak nystagmus with the head in a normal position was increased with abnormal positions, with sometimes a change in its direction, or nystagmus appeared with abnormal positions only. This phenomenon is transient. Electrolytic lesions of the tectal nuclei had a similar effect. In analysis of the receptor mechanism, neck reflexes and retinal reflexes could be excluded. Bilateral labyrinthectomy abolished the effect of position, while a weak spontaneous nystagmus might persist. The authors assume that the appearance of positional nystagmus after cerebellar lesions is a phenomenon of release of parts of the vestibulo-ocular reflex arcs, since it is associated with increase of the experimental postrotatory nystagmus. The experiments suggest that the existence of positional nystagmus should be tested routinely when a cerebellar lesion is suspected.

DRAYER, Philadelphia [ARCH. NEUROL. & PSYCHIAT.].

CURARE TREATMENT OF SPASTIC CHILDREN. ERIC DENHOFF and CHARLES BRADLEY, New England J. Med. **226**:411 (March 12) 1942.

A standardized, stable preparation of curare was injected intramuscularly in 6 children with cerebral palsy. The result was improved relaxation and reduction of spasticity in hypertonic muscles. Curare can be safely administered to children with cerebral palsy in individually adjusted doses that are larger than those previously suggested in the literature. These large doses are effective in reducing muscle spasm over a period of several days and require intramuscular injection but twice a week. Because curare relaxes the spasm of hypertonic muscles in doses insufficient to cause complete paralysis or respiratory embarrassment, treatment that is therapeutically efficient is not accompanied by the alarming symptoms

of threatened collapse, which are a constant threat with truly paralytic doses of the drug. However, in the present state of knowledge, efficiency combined with safety is attainable only when the dosage for each child is determined by noting the patient's response to each of several gradually increasing doses injected intramuscularly and starting at approximately 5 mg.

It is encouraging that in these 6 cases progress under physical therapy was definitely accelerated by curare. When amphetamine was added, the accomplishments of 4 of these children were even further increased because of the additional "drive" that was imparted by the latter drug. This is an effect noted in physically intact children, but it has not been noted before in spastic children.

There was no evidence that any tolerance to curare was established through its continued use. The response of individual patients to specific doses in a uniform fashion was outstanding.

GENGENBACH, Denver.

INFANTILE MUSCULAR ATROPHY OF SPINAL ORIGIN. J. G. MACLEOD and R. M. MACDONALD, Arch. Dis. Childhood **17**:30 (March) 1942.

The comprehensive term "infantile muscular atrophy of spinal origin" is used rather than Werdnig-Hoffman's disease and Oppenheim's disease. The condition presents the following features: (*a*) The disease is present at birth or develops gradually during the early months of life. (*b*) A familial incidence is common. (*c*) The sexes are equally affected. (*d*) The muscles are hypotonic, extremely so in some cases, and the tendon reflexes are lost. (*e*) Wasting of the muscles may be generalized or may be more prominent in certain areas, particularly in the trunk, neck and proximal segments of the limbs. It is often obscured by a thick layer of subcutaneous fat. (*f*) Paralysis of the intercostal muscles is common. Secondary results are a prominent abdomen, a weak cry, labored coughing and difficulty in sucking. (*g*) Rarely palsies of the cranial nerves occur. (*h*) Contractures develop in some patients. (*i*) The prognosis is poor. The majority of the patients die in a few months from pneumonia. A small number, especially infants with the congenital type, with a good family history and no local wasting tend to improve. (*j*) At autopsy the observations are atrophy of cells of the anterior horn and secondary atrophy of muscle.

Two cases are reported in detail, and attention is drawn to recent work with vitamin E in treatment of this condition.

KELLY, Milwaukee.

CEREBRAL ABSCESS DUE TO TRAUMA OF UNUSUAL ORIGIN. A. U. RAMON GUERRA and J. F. CASSINELLI, Arch. de pediat. d. Uruguay **13**:129 (March) 1942.

The authors report 3 cases of cerebral abscess caused by an unusual wound, the first in a child 21 months old who was attacked by a rooster thirteen days before admission to the hospital. He had received a penetrating head injury and died seven hours after admission to the hospital. Autopsy showed a scalp injury in the stage of healing, a right parietal bony perforation and localized suppurative leptomeningitis and acute cerebral abscess and intense cerebral edema of the right hemisphere.

The second case is that of a child 5 years old who also was attacked by a rooster. This child also had a lesion of the scalp. The second day after the injury a trephine showed a perforation of the occiput with injury to the dura and to the underlying peripheral tissue.

The wound was closed without drainage, and antitetanus and antigangrene serums were administered, as well as azosulfamide. There was complete cure in ten days.

The third case is that of a child 4 years old who also was attacked by a rooster and sustained an injury to the scalp. Within a few days a meningitis developed. This child was treated with a sulfonamide compound and antimeningococcus serum. It died on the twenty-second day after the injury, and at autopsy a suppurative leptomeningitis and a peripheral abscess opening in the left lateral ventricle were discovered.

SCHLUTZ, Chicago.

Psychology and Psychiatry

AMPHETAMINE (BENZEDRINE) SULFATE AS A CORRECTIVE FOR THE DEPRESSION OF SEDATIVE MEDICATION IN EPILEPSY. LEON J. ROBINSON, Am. J. Psychiat. **98**:215 (Sept.) 1941.

Robinson administered amphetamine sulfate in doses of 5 to 30 mg. to 58 patients with epilepsy who had manifested toxic symptoms due to anticonvulsant medication, chiefly with phenobarbital. These symptoms consisted of drowsiness, ataxia, irritability, aggressiveness, anorexia, vertigo, nystagmus and tremor. Thirty-nine of the 58 patients were relieved of their toxic symptoms by amphetamine sulfate, and to 21 of these 39 patients it was necessary

to administer the drug only temporarily. The frequency of seizures was not altered by the use of amphetamine. Robinson concluded that amphetamine sulfate is of especial value in allowing an increase in the anticonvulsant medication beyond that otherwise tolerated by the patient.

FORSTER, Boston. [ARCH. NEUROL. & PSYCHIAT.]

THE DEVELOPMENTAL STATUS OF SPEECH SOUNDS OF TEN FEEBLE-MINDED CHILDREN. ORVIS C. IRWIN, Child Development **13**:29 (March) 1942.

"This report represents the first step in a systematic study of the use of vowel and consonant elements by feeble-minded children. The purpose is to determine developmental trends in the speech of mentally retarded children and to relate data acquired in this field to the processes of development in normal infants and children and to the status of adult speech. Ultimately, information concerning the comparative rates of speech development in normal and feeble-minded children may be established and remedial measures for speech retardation may be set up. A further aim is to try out several indices of speech status on this type of data.

"Transcriptions of the speech of a group of ten low-grade feeble-minded children in a state institution were secured. The work was done during the first week of the year 1941. A second transcription of the sounds of these children was obtained on December 22, 1941. Approximately, then, a year had elapsed between the taking of the two samples.

"Although these data comprise only a segment of a broader research in the immature stages of human speech development, there are some conclusions which may reasonably be inferred from them. These are: Feeble-minded children use back vowels more infrequently than front vowels. In this respect their speech resembles that of young infants rather than that of adults. In consonant articulation the dispersion is trimodal whereas in young infants and adults the distributions are unimodal. The feeble-minded show a concentration in the labial, post-dental, and glottal regions while infants show the greatest piling up among the glottals, and adults among the post-dentals. The ratio of vowels to consonants in the speech sounds of this group of feeble-minded children is 1, whereas that of mature speech is 1 to 2. None of the ten subjects exhibits the mature ratio. The developmental status of the speech sounds of the group of four-year-old feeble-minded children, approximates that of normal children less than one year of age. The vowel ratio, the vowel-consonant ratio, and the profile are suitable tools for analyzing the speech sound status of retarded children."

[AUTHOR'S SUMMARY.]

THE CRITICAL EVALUATION OF THE VIENNESE TESTS AS APPLIED TO 200 NEW YORK INFANTS SIX TO TWELVE MONTHS OLD. DOROTHY S. ACKERMAN, Child Development **13**:41 (March) 1942.

"The purpose of this investigation was the application and validation of the Buehler Infant Tests for the second half of the first year of life, as presented in Buehler and Hetzer's 'Testing Children's Development.' Each of the four series for this period consists of ten items covering the five fields: bodily control, social behavior, learning, manipulation and mental production. The subjects were 200 infants, 100 girls and 100 boys divided equally at each level and according to descent into five groups: British, Italian, Jewish, Nordic and Slavic.

"Calculations were made of the developmental age (DA) and developmental quotient (DQ) analogous to the MA and IQ. A new feature introduced was the calculation of DAs and DQs for the five fields. The validation of the test series was sought in the distributon of the obtained scores. Internal consistency was studied by calculating and correlating the scores of two sets, odd-numbered versus even-numbered, both DAs and DQs, and by correlating the DQs in the five fields with the final DQ, for each child. Another study was that of the validity of the separate test items.

"The author concluded that the series seem to be a valuable instrument for estimating the development of infants for this period of life. Several substitutions in test items and in procedures were recommended."

[AUTHOR'S SUMMARY.]

SOME ASPECTS OF LEADERSHIP IN AN INSTITUTION. WILLIAM FAUQUIER and JOHN GILCHRIST, Child Development **13**:55 (March) 1942.

On the basis of questionnaires, rating scales and observation, leadership in an institution was investigated. A significant probable error between leader and follower groups was found to exist on a point rating scale. On the basis of data presented, the authors conclude "that

dominance, aggression, boldness, impulsiveness, excitability, and alertness find their most frequent expressions in the personality of the leader are facts inherent in the results of this study and in the observation of the activity of the boys."

[AUTHORS' SUMMARY.]

THE MANAGEMENT OF MENTALLY HANDICAPPED CHILDREN. BERT I. BEVERLY, Illinois M. J. **81**:408 (May) 1942.

A mentally handicapped child is one whose growth and development deviate from the average to such a degree that he fails to make an adjustment in his home, in public or private educational institutions and (or) in society.

Educable mentally handicapped children should be reared in their homes. State institutions are for uneducable children and for those who come to manifest uncontrollable behavior problems.

While there is a relation between mental deficiency and delinquency and dependency, the cause is primarily emotional.

Mentally retarded persons can have mental health as well as can those with normal intelligence. Mental health is based on security in parents and on allowing children to grow up according to their own individual patterns. Children then form habits of self reliance which give them confidence in their ability to face difficult situations.

Mentally handicapped children require especially trained teachers and special facilities in the school systems.

BARBOUR, Peoria, Ill.

THE PHOSPHORUS METABOLISM OF THE BRAIN AS MEASURED WITH RADIOACTIVE PHOSPHORUS. B. A. FRIES and I. L. CHAIKOFF, J. Biol. Chem. **141**:479, 1941.

In general it appears that the turnover of phosphatide in the brain is slow. Fries and Chaikoff have studied the metabolism of phosphorus in brain using radioactive p^{32}. The recovery of total radioactive phosphorus in the forebrain, cerebellum, medulla and spinal cord was compared at twenty-four and forty-eight hours after the administration of p^{32}. The highest recovery of p^{32} in all divisions of the central nervous system was found on the day of birth. From birth until the time the rat attained a weight of 50 Gm. a rapid decline in recovery of p^{32} was observed throughout the brain. As growth proceeded beyond 50 Gm. the decline continued, but at a much slower rate. The recovery of p^{32} was not uniform throughout the central nervous system. From birth until the time the rat attained a weight of 50 Gm., it was highest in the spinal cord or the cerebellum. After this the relative activities of forebrain, cerebellum and medulla rose steadily, and by the time a weight of 200 or 300 Gm. was reached the recoveries in the cerebellum, medulla and forebrain exceeded the recovery in the cord. The labeled phosphorus present as phosphatide did not account for more than 20 to 30 per cent of the total labeled phosphorus deposited in the brain.

PAGE, Indianapolis. [ARCH. NEUROL. & PSYCHIAT.]

A COMPARISON OF TEACHERS' DIAGNOSES OF MALADJUSTED CHILDREN, WITH CLINICAL FINDINGS. GEORGE D. LOVELL and HELEN D. SARGENT, J. Gen. Psychol. **60**:183 (March) 1942.

Attempts to find the best schoolroom atmosphere and the most favorable teaching technic are necessary to provide the child with an environment appropriate to his individual learning process. This responsibility falls largely on the classroom teacher.

This study is an attempt to determine how well the teacher is performing this function. The clinical material consists of children referred to the Northwestern Psychologic Clinic from the schools in the neighboring communities.

One hundred and twenty-nine children were referred because of poor schoolwork. Only 38 of these children were found by standard intelligence tests to have intelligence ratings below average. The cause of the poor schoolwork in the majority was found to be due to failure of personality adjustment.

The referring teachers were able to recognize social maladjustment in 50 per cent of those children given this diagnosis by the clinic. Other factors such as feelings of inferiority, family maladjustment and day dreaming were frequently found by the clinic to be the cause of poor learning. These important areas, however, were either not discerned or were considered irrelevant by the teachers.

WEINFELD, Highland Park, Ill.

CHILDHOOD SCHIZOPHRENIA. LAURETTA BENDER, Nervous Child **1**:138, 1942.

The author points out that childhood schizophrenia is a definite, recognizable syndrome. These children reveal a pathologic change which can be understood only "as a focal distur-

bance in pattern behavior that is reflected in a similar way through all levels and fields of integration and which tend to show a developmental curve." Dementia often occurs as an emergence of special abilities rather than as a deteriorating, regressive process as observed in the shut-in type.

BEVERLY, Chicago.

BIOGRAPHY OF A SCHIZOPHRENIC CHILD. CHARLES BRADLEY, Nervous Child **1**:141, 1942.

The author records a detailed history of a case of schizophrenia (in a girl) in which the condition was definitely diagnosed when she was 11 years of age. Although heredity and family background were good, the patient showed an aversion to strangers and other children during the early months of her life. Psychotherapy at home and in an institution as well as shock therapy and medication with amphetamine were used but apparently did not alter the course of the illness.

BEVERLY, Chicago.

TREATMENT OF SCHIZOPHRENIA OF CHILDHOOD. FRANCES COTTINGTON, Nervous Child **1**:172, 1942.

The author reports the methods of treating schizophrenia in childhood which are used at Bellevue Hospital. While results are discouraging, there is some evidence that the condition of some of these children may be improved.

BEVERLY, Chicago.

THERAPEUTIC PROCESS IN A CASE OF CHILDHOOD SCHIZOPHRENIA. JACK RAPOPORT, Nervous Child **1**:188, 1942.

This is the report of an extreme eating and behavior problem in an 11 year old boy who had signs of mental retardation but who probably had schizophrenia. His condition was greatly improved (the food problem straightened out) by play therapy (psychoanalytic technic as used by Melanie Klein).

BEVERLY, Chicago.

INSTINCT AND THE EGO DURING INFANCY. IVES HENDRICK, Psychoanalyt. Quart. **11**:33, 1942.

Hendrick discusses the part played by the instinct to mastery in the development of the child, together with its role in neurotic compulsion and the development of the ego. Infants under 2 years of age constantly learn to use their bodily tools for mastering the environment. In infants sexual fantasies and sexual play are common, as has been learned from direct observation and from reconstructions in the analyses of adults. The evidence from direct observation differs from that in reconstructions, since in the former the goal of the infantile erotism is not orgastic and the action itself is not compulsive; i. e., it does not culminate in orgastic satisfaction or in frustration with unrelieved tenson and conflict unless there is associated anxiety. All these phenomena appear as part of the reconstructions in the analyses of adults, since, Hendrick believes, the memory has been energized by the sexual instinct after puberty; in other words, the infantile memories which occur in analysis should be regarded as the critical end points of the infantile memories which have been repressed.

Mature behavior is the synthesis of various partial abilities. Each of these shows three stages in development: 1. The emergence of physiologic ability to form a reflex pattern, for example, sucking reflex. 2. A period of practice and training; for example, the child's ability to suck increases as he practices sucking. 3. The mature proficiency in the use of the act.

The first phase is stereotyped and is more closely related to specific stimuli than to any useful objective or emotional need. In the second phase there is a need to learn by repetition, which is independent of the specific stimuli and is followed by increasing ability to modify the stereotyped pattern. This learning process is the first objective appearance of the instinct to mastery and shows a compulsive need to practice the unlearned function. In the third phase there develops a proficiency in using the apparatus at will without further practice. The act is adapted to the use of the personality as a whole rather than as an exercise for its own sake. This adaptation is accompanied by an increasing degree of integration of all the partial functions. Later, compulsiveness consists of a regression to the normal stage of unlearned function and is associated with inability to exercise proficiently a function which gratifies the need to master. Undeveloped functions or those which are obstructed always provoke compulsiveness. This process of learning is the foundation of ego development. The more mature the ego the less evidence it shows of compulsive repetitiveness. This compulsive repetition is released (1) in the voluntary exercise of sensorimotor patterns before the capacity for efficient performance has been achieved by practice; (2) during the process of learning new patterns of a more complex nature prior to the attainment of efficient performance; (3) when the exercise of the mature function is disturbed by (*a*) external frustrations (by parents, the analytic transference neurosis and the limitations imposed by other persons or by a group),

(*b*) anxiety and guilt, (*c*) realistic anxiety (real dangers, traumatic neuroses and panic) or (*d*) survival of a dominant compulsive pattern of instinct discharge which is not subordinated to reality principle or the superego (negative therapeutic reaction and the compulsive personality), and (4) when functions essential to normal adult object relations (psychoses, psychopathy, ego defect neuroses) have not matured.

PEARSON, Philadelphia [ARCH. NEUROL. & PSYCHIAT.].

PHYSICAL DEFECTS IN THE GENESIS OF JUVENILE DELINQUENCY. FRITZ BLUMENTHAL, New York State J. Med. **41**:1749 (Sept. 1) 1941.

The influence of physical defects on personality and behavior is frequently forgotten. Changes in behavior are brought about through psychologic reactions to the defect. Delinquencies frequently have a close chronologic relationship to physical handicaps. Removal of the physical handicaps may correct or control the behavior problem.

AIKMAN, Rochester, N. Y.

PROGRESSIVE SYNDROME CONSISTING OF SYMMETRIC CUTANEOUS AND CONJUNCTIVAL TELANGIECTASES AND CEREBELLAR MANIFESTATIONS. LOUIS-BAR, Confinia neurol. **4**:32, 1941.

Louis-Bar reports the case of a child aged 9 who had a cerebellar syndrome and cutaneous manifestations, both of which had progressively developed from the age of 3 years. The manifestations of involvement of the nervous system consisted of ataxia, disturbance of speech and intellectual retardation. The skin showed telangiectatic areas and café au lait spots of fernlike distribution, and there were symmetric conjunctival capillary telangiectases. The author includes this case in the group of phacomas.

DEJONG, Ann Arbor, Mich. [ARCH. NEUROL. & PSYCHIAT.]

THE PSYCHISM OF INFANCY, PUBERTY, AND ADOLESCENCE. MANUEL TÁBOAS GONZÁLEZ, Arch. de med. inf. **11**:68 (April-June) 1942.

Gonzales presents a short résumé of the principal conditions in the mental states of infancy, puberty and adolescence.

SANFORD, Chicago.

THE PSYCHIC FACTORS IN THE DYSTROPHY OF INFANTS. M. L. SALDUN DE RODRIGUEZ, Arch. de pediat. d. Uruguay **13**:150 (March) 1942.

Psychic factors can produce pronounced repercussion in the general condition and especially in the nutritional state of an infant. The psychic shocks do not always stand in relation to the economic conditions or the comfort of the home, but are referable more to the psychic conditions of the family.

The problem often presents itself in infants placed with foster parents of the white race, but it particularly occurs with infants under the care of Negro nursemaids or colored half-breeds.

The condition is observed most frequently in infants around the age of 1 year and after. The author has never seen it in an infant under the age of 6 months. The problem can be met by proper prophylactic and therapeutic measures.

SCHLUTZ, Chicago.

THE VOCABULARY USED BY DELINQUENT GIRLS. B. GABY, Bol. serv. Soc. d. Menores **2**:36 (March) 1942.

This article contains slang terms used by delinquent minors (female). Any one wishing to become familiar with the vernacular of ragamuffins of Spanish and Portuguese America will find this interesting.

SANFORD, Chicago.

UNSTABLE INFANTS. JEAN WINTSCH, Ztschr. f. Kinderpsychiat. **8**:65 (Sept.) 1941.

Various phases of the unstable, nervous child are presented. The symptoms are evaluated in the light of a hyperactive nervous system.

JAHR, Omaha.

NIGHT TERRORS (PAVOR NOCTURNUS). L. VON PÁTZAY-LIEBERMANN, Ztschr. f. Kinderpsychiat. **8**:74 (Sept.) 1941.

General features of night terrors are discussed. An interesting case is cited, that of a 5 year old boy who was suffering from repeated night terrors traceable to shock following a herniotomy at the age of 2 years followed by an accident at 3 years. The treatment consisted of reeducation through psychotherapy.

JAHR, Omaha.

PSYCHIATRIC STUDIES ON A SERIES OF TWINS. ERIK ESSEN-MÖLLER, Acta psychiat. et neurol. (supp. 23) **8**:1, 1941.

Using Luxenburger's method of complete series, Essen-Möller examined 69 pairs of twins of the same sex among 10,000 patients in Swedish hospitals for mental disease. The author saw personally both twins of 41 pairs and one twin of a mother of 19 pairs. The question whether the twins were monozygotic or dizygotic was determined on the basis of physical resemblance, with the aid of descriptions, photographs and, if possible, examination. Twenty-one pairs were monozygotic and 48 dizygotic. The monozygotic pairs are described and discussed in detail (a table with photographs is given) and questions of characterologic features and environmental and constitutional differences are dealt with in special chapters. The author gives a summary of his cases, which is translated verbatim, as his classification and diagnostic conclusion are not identical with prevalent American views.

Survey of Monozygotic Twins

	Twins	Patient's Psychosis	Twin	
			Psychosis	Characterologic Anomalies
1	Anton and Karl	Schizophrenia	Borderline	Present
2	Agnes and Berta	Schizophrenia	Reactive, with schizophrenic features	Present
3	Alfred and August	Schizophrenia	None	Present
4	Anselm and Konrad	Reactive psychosis and schizophrenia	Reactive state; induced	Present
5	Frida and Hanna	Schizophrenia	Depressive state; hallucinosis	Present
6	Julia and Ida	Schizophrenia	None	Present
7	Martha and Rosa	Schizophrenia with manic features	Depressions with schizophrenic symptoms	Present
8	Jenny and Klara	Nonsymptom states with excitement and anxiety; schizophrenic group	None	Absent (?)
9	Erika and Helena	Nonsymptom depressions, partly reactive; schizophrenic group	Psychosis with schizoid defects	Present
10	Rolf and Herbert	Reactive querulence with delusions of reference	None	Present
11	Hans and Rudolf	Senile schizophrenia	None	Present
12	Otto and Ragnar	Schizoid state after trauma	None	Present
13	Ernst and Holger	Cyclic phases of post-traumatic psychosis	None	Absent
14	Laura and Helga	Asthenic depression in hypertension	None	Present
15	Hilma and Blenda	Endocrine disturbance; reactive psychosis	None	Absent
16	Maria and Gerda	Endocrine disorder; reactive psychosis	None	Absent
17	Lina and Fanny	Manic-depressive and migrainous psychosis	Borderline	Absent (?)
18	Aina and Ester	Epilepsy with psychosis	None	Present
19	Selma and Astrid	Epilepsy with psychosis	None	Absent (?)
20	Alma and Tekla	Postchoreatic psychosis of exhaustion	None	Present (?)
21	Werner and Magnus	Dementia paralytica	None	Absent

On the basis of this classification, the author finds a psychotic second twin in only 7 of his 21 monozygotic pairs, among whom were 1 with dementia paralytica, 1 with post-traumatic psychosis, 1 with postchoreatic psychosis, 2 with doubtful endocrine disorders and 1 with hypertension. In the first 10 pairs of psychotic twins one member was schizophrenic, and in at least 5 of these (pairs 1, 2, 5, 7 and 9), not in just 1 of 7 pairs, as the author states, the other twin was also schizophrenic.

The author points to the frequency and constancy of characterologic anomalies and psychopathic features of the twin in a large number of his original 21 pairs of psychotic twins. He believes that genetic studies prove that a differentiation between psychotic and psychopathic and schizophrenic and schizoid is not important.

Only in the cases of Otto, Ernst, Alma and Werner does the author see clear environmental factors. In the other cases the influence of the environment was problematic. In 3 pairs there was no difference of environment, but the partners developed very differently. In 6 pairs characterologic differences developed before changes in the environment occurred. In many cases of hereditary "endogenous" psychoses it is likely, in view of quantitative expressions of characterologic anomalies, that environmental factors operate at very early stages in ontogenesis.

REDLICH, Boston. [ARCH. NEUROL. & PSYCHIAT.]

CASE OF STURGE-WEBER'S DISEASE. MARGARETE LOMHOLT, Ugesk. f. læger **103**:613 (May 8) 1941.

The patient was a full term girl of 14 months. Parturition had been normal. Right-sided hemiplegic paralysis was observed at 2 months of age; she had had convulsions since 3 months of age. There were an extensive hemangioma principally over the left side of the body and strabismus without other ophthalmic symptoms. There was slight mental debility. Roentgen examination revealed a walnut-sized gyriform conglomerate of calcifications in the cortex cerebri at the posterior cranial fossa.

WALLGREN, Göteborg, Sweden.

Diseases of the Genitourinary Tract

THE USE OF SULFANILAMIDE IN THE TREATMENT OF ACUTE GLOMERULAR NEPHRITIS. ROBERT H. WILLIAMS, WARFIELD T. LONGCOPE and CHARLES A. JANEWAY, Am. J. M. Sc. **203**:157 (Feb.) 1942.

A comparative study has been made of the course of acute hemorrhagic nephritis in a group of 42 patients treated in essentially the same manner as a group of 108 similar patients except that to the former group sulfanilamide was administered. Most of these patients have been followed from two to five years or longer.

The results indicate that in the subjects receiving sulfanilamide the foci of infection have cleared up more rapidly, the signs of renal damage have disappeared more rapidly, the exacerbations of the nephritis following tonsillectomy have occurred less frequently, the duration of the edema and hypertension has been shorter and the clinical recoveries have been more rapid and more numerous.

HENSKE, Omaha.

URINARY INFECTIONS IN CHILDHOOD. EDWARD W. WHITE and CHARLES A. MURRAY, Illinois M. J. **81**:144 (Feb.) 1942.

With but few exceptions children may fall heir to every urologic disease known to exist in adults. In many instances major uropathy begins in infancy or early adult life; hence the study of urinary infections in the young is worthy of grave consideration. The recognition and adequate treatment of accessory causes of persistent infections of the urinary tract in childhood is essential for proper management.

Usually acute infections of the urinary tract properly recognized are self limited and disappear clinically in from two to four weeks, irrespective of treatment. Infection of the renal parenchyma is the dominant lesion. Although acute urinary diseases are directly produced by some bacterial invasion, there are a multitude of predisposing factors. Urinary stasis plus obstruction seems to be the most potent predisposing factor. Bacterial invasion through the medium of toxemia and trauma is another common factor. Of the gram-negative bacteria found, Bacillus coli communis is the most common. Of the gram-positive bacteria, staphylococci are of the highest incidence, with streptococci next.

The path of renal disease in infancy and early childhood is in most instances hematogenous. The simple degenerative change called cloudy swelling is the most common pathologic change in the kidneys during the course of acute infectious diseases in children. Another pathologic change observed recently is the precipitation of crystals of sulfanilamide in the renal tubules.

BARBOUR, Peoria, Ill.

CONGENITAL HYDRONEPHROSIS IN THE LOWER HALF OF A DOUBLE KIDNEY. SIDNEY FEYDER and CLYDE L. DEMING, New England J. Med. **226**:220 (Feb. 5) 1942.

The 5 year old boy patient was said to have had from birth a protuberant abdomen, which had been growing steadily larger. The left side of the abdomen was larger than the right and was occupied by a smooth cystic mass filling the left flank from the costal margin to the iliac crest and extending to well beyond the midline on the right. The remainder of the physical examination revealed no abnormalities.

Accessory laboratory data were within normal limits. Gastrointestinal roentgenograms showed the stomach to be displaced upward and to the right, with small and large intestinal loops pushed into the right half of the abdomen and the descending colon swinging in a curvilinear line over to the right.

Review of the intravenous and retrograde studies indicated a massive hydronephrosis in the lower segment of a double kidney, with complete destruction of functioning renal tissue in that pole, associated moderate hydronephrosis in the upper segment and an incomplete

reduplication of the ureter. The patient was operated on through a left lumbar incision and the cystic mass approached posterolaterally. Two thousand cubic centimeters of straw-colored fluid was aspirated. Because of a complex arterial blood supply, heminephrectomy was not done.

Two ureters were found, one entering the cystic mass below and the other extending upward to enter a separate pelvis at the upper pole. The ureters were separate to a point about 5 cm. above the bladder, where they joined. Following operation, the patient made an uneventful convalescence.

In reviewing a series of 101 cases of hydronephrosis in infancy and childhood, Kretschmer found the highest incidence in the age group from 5 to 7 years, 28 per cent occurring in this range. Of the various causes of hydronephrosis in this series, 24 per cent were associated with congenital anomalies of the kidney and ureter. GENGENBACH, Denver.

THE TREATMENT OF GONOCOCCAL VAGINITIS IN CHILDREN WITH DIETHYLSTILBESTROL. J. D. WOODRUFF and R. W. TELINDE, South. M. J. **35**:389 (April) 1942.

The authors report that gonococcic vaginitis can be successfully treated with the synthetic estrogen diethylstilbestrol. The substance may be given by oral administration as well as by suppositories, but results are more rapidly obtained with the latter.

The optimum dose by mouth was found to be 1 mg. per day, whereas 0.1 mg. used as a daily suppository was adequate to effect a cure in all cases except 1 in which it was used. Nausea and vomiting occurred in an appreciable percentage of the cases in which the drug was given by mouth. In no case did this occur when it was given by suppository.

Systemic effects, such as enlargement of the breasts, uterine enlargement and growth of pubic hair, were noted in various percentages in the cases in which the patient received the drug by mouth. The only systemic effect noted in the group treated with suppositories was enlargement of the breast, which occurred in 13 of 29 cases. The enlargement regressed in all cases in from four to six weeks.

The authors believe that the use of suppositories is the method of choice in administering diethylstilbestrol in the treatment of gonococcic vaginitis in children and that a suppository containing 0.1 mg. is an adequate dose. SCHLUTZ, Chicago.

LATE RESULTS OF PLASTIC SURGERY IN HYDRONEPHROSIS. T. D. MOORE, South. M. J. **35**: 425 (May) 1942.

The author had the best results with high insertion of the ureter in which either a lateral anastomosis or a Foley type of "Y" operation had been performed.

Of the 6 cases in which aberrant vessels apparently were causing obstruction, and simple division and ligation of vessels was performed in 4, the late results were somewhat disappointing when judged by the postoperative pyelographic evidence. In the remaining 2 cases, in which the ureter was reimplanted with or without division of the vessels, the results were more encouraging.

An excellent result is reported in 1 instance of fibrosis of the ureteropelvic juncture for which a Rammstedt type of operation was performed; and in another case in which the obstruction was of a similar type, a failure resulted from underestimating the importance of an adynamic ureter. In all cases in which a prolonged period of ureteral splinting and nephrostomy drainage was employed, for at least six weeks the results were uniformly satisfactory. The importance of these measures cannot be overemphasized. SCHLUTZ, Chicago.

ANEMIA IN NEPHRITIS. PATRICK MACARTHUR, Arch. Dis. Childhood **17**:1 (March) 1942.

Previous work on anemia in nephritis is discussed. In edematous patients blood obtained by puncture of the lobe of the ear is slightly diluted, but the errors arising in doing counts from blood obtained by venipuncture are greater than those arising from puncture of the skin, and the latter method is therefore preferable. During the stage of increasing edema and active diuresis in acute nephritis there is a concentration of blood. In neither of these types of nephritis is there more than slight anemia. When certain acute infections occur in the course of nephrosis, rapid and severe anemia results; and after effective treatment of the infection the blood quickly returns to normal. Anemia is not characteristic of nephrosclerosis in the absence of hemopoiesis. In chronic hemorrhagic nephritis there is often

severe orthochromic normocytic anemia with a normal or slightly increased number of reticulocytes and an increase in leukocytes. The blood picture is not that of aplastic anemia. No treatment that will influence the condition is known. It is only in this type of nephritis that true anemia has been found.

KELLY, Milwaukee.

SOME ASPECTS OF THE BLOOD CHEMISTRY OF THE NEPHRITIC CHILD. ANNE E. SOMERFORD, Brit. J. Child. Dis. **39**:1 (Jan.-March) 1942.

The blood chemistry of 9 children with enuresis was found to be normal.

Twenty-two nephritic children were studied. Ten were in the initial or acute stage; 9 of these were discharged much improved, and 1 died.

Twelve children were classified as being in the chronic stage. Two of these died and 1 was rapidly deteriorating.

A brief summary is given of each case.

The author recommends that in the acute stage the urea content of the blood should be estimated at weekly intervals and in the chronic stage the urea and creatinine clearances (particularly the latter).

In both the acute and the chronic phases the serum calcium, blood phosphorus and plasma albumin and globulin should be determined.

LANGMANN, New York.

TREATMENT OF THE NEPHROTIC SYNDROME WITH SERUM TRANSFUSIONS: A REPORT TO THE MEDICAL RESEARCH COUNCIL FROM THE N.W. AND S.W. BLOOD SUPPLY DEPOTS. H. BROWN, C. H. GRAY and P. L. MOLLISON, Brit. M. J. **1**:515 (April 25) 1942.

For 12 patients, all of whom had marked edema, the use of concentrated plasma was tried in an effort to relieve the edema. Eight of these patients were considered as having chronic nephritis in the nephrotic stage. One had so-called true nephrosis: 1 had amyloid nephrosis, and the condition of 2 was due to malabsorption of protein from the alimentary tract. The transfused material was reconstituted from the dried plasma which was obtained from the Medical Research Council. The usual concentration of the serum was approximately four times that in the normal blood. It was noted that febrile reactions occurred in several patients and that 2 patients had rather severe pains in the back. Determinations of the concentrations of hemoglobin and of serum proteins were done for all patients. The results were not satisfactory. In the cases of nephrotic syndrome secondary to chronic nephritis only 2 patients responded after the transfusion. In both of these cases several transfusions were used, and after a period of diuresis the edema returned again in from ten to fourteen days. In one of the cases at the appearance of the second attack of edema no response was obtained from transfusions of concentrated serum. In the case of amyloid nephrosis some slight improvement was noted after transfusion of concentrated serum, but this was only temporary and was not regarded as successful treatment. In 5 of the cases no good effect could be noted, and in 2 of the cases edema increased after transfusion. The complete case histories of each patient are contained in the article. Immediately after transfusion of concentrated protein, the serum protein level was generally found to have risen and the hemoglobin level to have fallen. However, twenty-four to forty-eight hours after this the serum protein concentration was no greater than it was before transfusion and the hemoglobin had usually returned to the pretransfusion level.

In the conclusion the authors state "it appears that in the nephrotic stage of glomerulonephritis a transfusion of concentrated serum is as likely to be followed by an adverse as by a favourable effect."

BIRDSONG, University, Va.

CONGENITAL ABNORMALITIES OF THE GENITO-URINARY SYSTEM. M. G. SUTTON, M. J. Australia **1**:370 (March 28) 1942.

Sutton's article is a postgraduate lecture presenting a fine discussion of each of the many congenital abnormalities of the genitourinary system commonly and uncommonly encountered in urologic practice.

GONCE, Madison, Wis.

TRANSITORY PUBERAL HYPOGENITALISM. F. ROCCA and R. BUCETA DE BUÑO, Arch. de pediat. d. Uruguay **13**:284 (May) 1942.

The authors studied various clinical types of puberal hypogenitalism. They were as common in the female as in the male. In general they seemed to be of glandular origin and due to simple or multiple glandular deficiencies. The types which were usually found can be divided into those showing obesity of the type of Froehlich and those showing generalized

obesity accompanied by hypogenitalism. Absence of secondary sex characteristics and sometimes delayed synostosis are present.

Some patients showed the clinical symptoms of hypogenitalism accompanied by asthenia, with excessive height and eunuchoid proportions. Others showed dwarfing accompanied with hypogenitalism. Both the hypogenitalism and the dwarfing tended to be corrected and became normal with the development of puberty.

SCHLUTZ, Chicago.

Diseases of the Ductless Glands; Endocrinology

ACTIVATED STEROLS AND CALCIUM SALTS IN TREATMENT OF PARATHYROID TETANY. ELMER L. SEVRINGHAUS, Am. J. M. Sc. **203**:726 (May) 1942.

Comparisons on 4 patients with tetany indicate that large doses of vitamin D may serve to control serum calcium and phosphorus levels adequately but that at current prices this entails an increase in cost to the patient of two to six times that required for similar success with use of dihydrotachysterol.

Use of calcium in the form of the chloride is advocated, and its superior efficiency in furnishing calcium is combined with safety and palatability when the salt is dispensed as a 25 per cent solution in the syrup or elixir of glycyrrhiza.

HENSKE, Omaha.

ADRENAL NEUROBLASTOMA WITH ORBITAL METASTASES. G. P. GUIBOR, Am. J. Ophth. **25**: 387 (April) 1942.

Guibor gives the following summary:

"1. A typical case report, with autopsy, of a seven-month-old infant with a right adrenal neuroblastoma is presented. This neoplasm was so malignant and grew so rapidly that lymphatic metastases were found in the retroperitoneal and mediastinal lymphatics, about the tongue and tonsils, in the orbit, maxilla, base of skull, and dura mater. The primary tumor could not be palpated and was found only at autopsy.

"2. The difficulty in diagnosing the malady is that usually found in cases of Hutchinson neuroblastoma. It simulated a sarcoma of the orbit or skull. Roentgenograms suggested a hemangioma or meningioma. The blood examination suggested chloroma.

"3. Even though the primary neoplasm was in contact with the liver, the brain, and the kidney, it did not invade these organs by contiguity but metastasized through the lymphatics to more distant tissues.

"4. The roentgenographic sun-ray pattern seen in X-ray plates of the left temporal bone has not been reported previously.

"5. The microscopic picture is typical of a neuroblastoma of the adrenal."

W. S. REESE. [ARCH. OPHTH.]

CHANGES IN BLOOD CHEMISTRY ASSOCIATED WITH CIRCULATORY FAILURE IN THE ADRENALECTOMIZED DOG. J. W. REMINGTON, V. A. DRILL, W. KLEINBERG and W. W. SWINGLE, Endocrinology **30**:692 (May) 1942.

The healthy adrenalectomized dog will develop a fatal circulatory collapse within five to twelve hours after being subjected to any of a wide variety of types of stress. This peripheral vascular failure can be prevented by the administration of liberal amounts of cortical extract.

This paper reports the qualitative differences in the effects when cortical extract is replaced by crystalline adrenal steroids.

"None of the blood chemistry findings reported give a direct explanation of the underlying deficiencies concerned in the circulatory collapse which follows the stress procedures. Several lines of evidence, including changes in blood sugar, indicate that a deep-seated disturbance in carbohydrate metabolism affecting the functional capacity of the tissues of the body may be present."

JACOBSEN, Buffalo.

ACTION OF VASOPRESSIN AND OXYTOCIN IN CAUSING PREMATURE OVIPOSITION BY DOMESTIC FOWL. W. H. BURROWS and R. M. FRAPS, Endocrinology **30**:702 (May) 1942.

Premature oviposition of hard-shelled eggs is effected in the hen by intravenous injection of pitressin or pitocin.

JACOBSEN, Buffalo.

PROGESTERONE-LIKE ACTIVITY OF SOME STEROID COMPOUNDS AND OF DIETHYLSTILBESTROL IN STIMULATING MAMMARY LOBULE-ALVEOLAR GROWTH. JOHN P. MIXNER and CHARLES W. TURNER, Endocrinology **30**:706 (May) 1942.

It has been shown that progesterone stimulates progestational proliferation of the uterus and growth of the mammary lobule-alveolar system in the guinea pig. In this paper it is shown that desoxycorticosterone acetate, dehydroandrosterone, diethylstilbestrol, acetoxypregneninolone and methyl testosterone have similar but lesser effect on mammary growth.

Testosterone and testosterone propionate in doses up to 10 mg. failed to stimulate lobule-alveolar growth.

JACOBSEN, Buffalo.

STUDIES CONCERNING THE MECHANISM CONTROLLING THE INITIATION OF LACTATION AT PARTURITION: I. CAN EXTROGEN SUPPRESS THE LACTROGENIC HORMONE OF THE PITUITARY? JOSEPH MEITES and C. W. TURNER, Endocrinology **30**:711 (May) 1942.

Experiments here reported suggest that the apparent decrease in lactation which has been reported in some animals with large injections of estrogenic hormone and which was secured by the authors in rats treated with diethylstilbestrol and testosterone propionate is probably due to a decrease in secretion of anterior pituitary hormones other than lactogen. These anterior pituitary hormones are believed to influence the yield of milk through their action in depressing the availability of the precursors of milk in the blood rather than the potential function or capacity of the mammary epithelium to secrete milk.

JACOBSEN, Buffalo.

STUDIES CONCERNING THE MECHANISM CONTROLLING THE INITIATION OF LACTATION AT PARTURITION: II. WHY LACTATION IS NOT INITIATED DURING PREGNANCY. JOSEPH MEITES and C. W. TURNER, Endocrinology **30**:719 (May) 1942.

In guinea pigs progesterone alone had no effect on the lactogen content of the pituitary gland. Estrone alone elicited definite increases in the lactogen content of the pituitary. Suitable combinations of progesterone and estrone either entirely prevented or reduced the increase in lactogenic hormone which could be obtained with estrone alone. It is thought that this inhibiting action of progesterone explains the fact that lactation does not commence during pregnancy.

JACOBSEN, Buffalo.

STUDIES CONCERNING THE MECHANISM CONTROLLING THE INITIATION OF LACTATION AT PARTURITION. JOSEPH MEITES and C. W. TURNER, Endocrinology **30**:726 (May) 1942.

In this paper evidence is submitted showing that the diminution or cessation of progesterone secretion just prior to parturition permits estrogen to assume the ascendency and quickly stimulate an increased elaboration of lactogenic hormone, which, in turn, brings about the onset of lactation.

JACOBSEN, Buffalo.

CONDITIONS MODIFYING THE EFFECTIVENESS OF TESTOSTERONE, TESTOSTERONE PROPIONATE, AND METHYL TESTOSTERONE. R. R. GREENE, M. W. BURRILL, E. OPPENHEIMER and D. NELSON, Endocrinology **30**:734 (May) 1942.

When testosterone, testosterone propionate and methyl testosterone are administered subcutaneously, percutaneously in various vehicles and in the form of implanted pellets different degrees of effectiveness are noted, the implantation of pellets being the most effective method.

JACOBSEN, Buffalo.

BLOOD LIPIDS OF THE HYPOPHYSECTOMIZED-THYROIDECTOMIZED DOG. C. ENTENMAN, I. L. CHAIKOFF and F. L. REICHERT, Endocrinology **30**:802 (May) 1942.

The thyroid gland exerts a definite control over lipid metabolism. The concentration of lipids in the blood, especially esterified cholesterol and neutral fat, is elevated after thyroidectomy. It has also been found that hypophysectomy alone has but little effect on the levels of the lipids in the blood of dogs. The present communication shows that hypophysectomy does not inhibit the rise in the blood lipids produced by thyroidectomy.

The uniformly striking and rapid increases in the concentration of blood lipids that occurred after removal of the second gland (i. e. the thyroid gland) as compared with the slight and irregular response after hypophysectomy alone suggest that an acute deficiency of the thyroid hormone per se is responsible for the high concentration of the blood lipids in the hypophysectomized-thyroidectomized dog.

JACOBSEN, Buffalo.

ONE VERIFIED AND ONE PROBABLE CASE OF SYMPATHOMA IN CHILDHOOD. P. DE ELIZALDE, P. R. CERVINI and R. P. BERANGER, Arch. de pediat. d. Uruguay **13**:201 (April) 1942.

The authors report a case in which they believe are shown the symptom complex and pathologic changes of a sympathoma. At the age of 1 month the infant showed an embryonal sympathoma of the right adrenal capsule with a metastasis to the liver.

The tumor conformed to the clinical type described by Pepper. Puncture of the tumor masses showed the presence of blastomatous cells. The condition of chloroma was also considered in this case.

SCHLUTZ, Chicago.

NEW CONCEPTS IN THE TREATMENT OF CHILDHOOD DIABETES. H. CANTONNET and P. CANTONNET, Arch. de pediat. d. Uruguay **13**:220 (April) 1942.

The authors discuss the newer forms of treatment of diabetes as formulated by Joslin P. White and Escudero. These differ from the older forms of treatment mainly by the high caloric diet, rich in carbohydrates.

The older forms of diet were poor in carbohydrates and deficient in caloric intake and often caused an arrest of growth. The newer treatment leads to greater gain in weight, height and physique and makes the diabetic child conform more to the normal in development.

The authors discuss the discovery by Hagedorn in 1936 of the treatment of juvenile diabetes with protamine zinc insulin. This treatment is now generally advised as one of the best and most effective forms of treatment of juvenile diabetes and in most instances gives excellent results.

Protamine zinc insulin corrects the glycemic lability of the diabetic child and on account of its slow and prolonged action prevents the nocturnal hyperglycemia which is so often observed when simple insulin was used. The use of protamine zinc insulin commonly makes unnecessary the use of additional injections of simple insulin.

SCHLUTZ, Chicago.

ALTERATIONS OF THE CELLULAR PERMEABILITY TO POTASSIUM AND WATER PRODUCED BY SUPRARENAL CORTEX. V. H. CICARDO, Rev. Soc. argent. de biol. **18**:79 (May) 1942.

Perfusion of the muscles of an adrenalectomized toad with potassium-free Ringer's solution produces an intense edema; the potassium content of the perfusate is higher than that yielded by controls not operated on. Desoxycorticosterone acetate decreases slightly the concentration of potassium in the perfusate of normal toads and also the degree of edema. Depletion of cellular potassium through increased permeability of the cell boundary is competent to explain many of the features produced by adrenal deficiency. This topic is discussed synoptically.

MCCUNE, New York.

THE EFFECT OF PITRESSIN ON THIRST IN DIABETES INSIPIDUS. Q. PASQUALINI and A. AVOGRADO, Rev. Soc. argent. de biol. **18**:88 (May) 1942.

"In two cases of diabetes insipidus the injection of 5 units of the pressor hormone of posterior pituitary produced the disappearance of thirst in 20 minutes even if water was not given. This suggests that the pressor hormone might exert some action on other tissues besides its antidiuretic action on the kidneys, perhaps on the central receptors of thirst."

MCCUNE, New York.

Diseases of the Muscles, Bones, Joints and Lymph Glands

THE EFFECT OF ROENTGEN RAYS UPON THE GROWING LONG BONES OF ALBINO RATS: QUANTITATIVE STUDIES OF THE GROWTH LIMITATION FOLLOWING IRRADIATION. CHARLES HINKEL, Am. J. Roentgenol. **47**:439 (March) 1942.

Seventy-three per cent of postnatal femoral growth in albino rats takes place at the distal extremity of the bone. The growth rate is such that there is a constant linear relationship between the logarithm of bone length and the reciprocal of age.

Roentgen rays applied to the growing epiphysial region produce quantitatively predictable degrees of stunting, ranging from temporary retardation to permanent cessation of growth, depending on the dose. Controlled stunting by radiation is temporary. After a latent period there is diminution of growth rate, but measurable growth soon reappears. Young animals recover more quickly than older animals and can tolerate quantities of roentgen rays far in excess of the minimal stunting dose. Months after irradiation with large doses there is

no evidence of bony decalcification. Microscopic studies show a return to normal cartilage and bone architecture, and absence of permanent injuries to the marrow or blood vessels in young animals.

This method involving artificial retardation of bone growth may prove to be applicable for clinical usage when it is deemed advisable to equalize the lengths of asymmetric bones.

SQUIRE, Chicago.

VALUE OF CHEMOTHERAPY IN THE TREATMENT OF OSTEOMYELITIS. ABRAHAM O. WILENSKY, Arch. Surg. **44**:234 (Feb.) 1942.

The clinical effect of sulfanilamide and its derivatives as chemotherapeutic aids in the treatment of the various forms of osteomyelitis has been thoroughly reviewed. The routes of administration, namely, oral, rectal, subcutaneous and intravenous, have been studied. The reports in the literature dealing with the local use of chemotherapy have been analyzed. The effectiveness of the drugs in the various types of osteomyelitis has been noted. It is pointed out by the author that the published reports are not in agreement as to the value of chemotherapy for this disease. The results of chemotherapy are not predictable. In actual practice, the treatment of osteomyelitis with sulfanilamide and its derivatives has not produced the startling results which it has had in the treatment of some medical conditions, notably the various types of pneumonia. The observed results have varied all the way from the absolutely negative to occasional satisfactory effects. These drugs, as a rule, have not prevented the spread of the disease or the occurrence of complications. In spite of these uncertain results, chemotherapy is indicated along with the surgical treatment of the disease.

KAISER, Rochester, N. Y.

CONGENITAL DEFORMITIES IN THE REGION OF THE FORAMEN MAGNUM: BASILAR IMPRESSION. WILLIAM T. PEYTON and HAROLD O. PETERSON, Radiology **38**:131 (Feb.) 1942.

Basilar impression, platybasia and basilar invagination are terms used to designate a deformity of the bony structures about the foramen magnum. As to cause, it has been variously considered as due to hydrocephalus, trauma, rickets or Paget's disease or as a congenital anomaly, with the majority of the evidence in favor of the last. The condition is said to be more common among Eskimos. Of a total of 26 cases collected from the literature and an additional 3 cases reported by the authors, males were affected in 17 and females in 11; in 1 case the sex was not given. The age at the time of examination varied from 17 to 70 years, the average being 34 years.

Many types of anomalous development occur about the base of the occipital bone and the upper cervical portion of the spine, and of these basilar impression is one of the most extensive. The other anomalies, such as defects of the posterior arch of the atlas, fusion or absence of the cervical vertebrae, assimilation of the atlas and manifestations of an occipital vertebra, may occur alone or as part of the features of basilar impression. All reports of cases of basilar impression in which the specimen has been dissected show that assimilation of the atlas is a constant part of the condition. This suggests that it represents an extreme grade of a group of anomalies which may occur in this region and that they are all more or less related.

Basilar impression may be present without symptoms, but when symptoms are present they develop in adolescence or late in life. They are slowly progressive, and the condition is frequently fatal. The symptoms are so variable that a diagnosis can rarely be made in life without roentgenographic verification. The clinical manifestations may be divided into two categories: the skeletal and the neurologic. The skeletal signs consist of a short neck, with the head shifted downward between the shoulders and tilted backward, and restricted movements of the head on the neck. The neurologic signs consist of irritation and paralysis of the cervical nerves and tracts of the spinal cord, due to compression at or near the foramen magnum; irritation or paralysis of the cranial nerves in the posterior fossa; compression of the medulla by the odontoid process; cerebellar disturbances, due to compression of the cerebellum in the shallow posterior fossa and, finally, increase in intracranial pressure.

Since basilar impression consists of anomalies of the occipital bone and upper cervical portion of the spine, it is best recognized by roentgenographic examination; a lateral view of the cervical portion of the spine, including the base of the skull, is sufficient for diagnosis. The authors believe that in all cases there is some degree of assimilation of the atlas, with fusion of the posterior arch with the occipital bone apparent in the lateral view. Chamberlain advocates drawing a line from the posterior edge of the hard palate to the posterior lip of

the foramen magnum. If the odontoid process projects above this line basilar impression may be suspected. The authors agree with the correctness of this observation but find it hard at times to identify the structures in question. Changes in the basilar angle are inconstant, and alterations in the medial part of the petrous pyramids often are not present or are inconspicuous. Decrease in size and distortion of the foramen magnum are constantly seen, but may be extremely hard to demonstrate roentgenographically, owing to inability to place the patient in a position to demonstrate this because of his short and relatively immobile neck. Laminagraphy may help.

In 23 cases it was possible to determine the age of onset of symptoms, the average being 29 years. Neurologic symptoms were present in 25 cases, causing death in 10, and were absent in 4. Operation was performed in 8 cases, the operation of choice being suboccipital craniotomy and laminectomy of the upper cervical vertebrae. Cases in which operation has been performed are too few to permit of conclusions, but if it is found that such a procedure will prevent the progression of symptoms, even if there is not always restoration of function, the concept of basilar impression as a fatal disease will need to be revised.

KENNEDY, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

SPONDYLITIS ADOLESCENS: STRÜMPELL-MARIE DISEASE. HARRY C. BLAIR, Surg., Gynec. & Obst. **74**:663 (March) 1942.

Synonyms for this disease are Strümpell-Marie disease, Bechterew's disease, ankylosing spondylitis, *spondylose rhizomélique* and spondylitis ankylopoietica. The clinical course is long, starting early in life with pain in the lower part of the back. This may begin as early as the age of 12 years, and ankylosis may not take place until the patient is 25 years old or more. Roentgenograms show advanced changes in the sacroiliac joint. The erythrocyte sedimentation rate is increased in proportion to the extent of involvement. This does not necessarily indicate that the cause is focal infection, since the disease occurs in cases in which there is no evidence of focal infection or in which all sources of infection have been removed. A metabolic disturbance is apparently not the cause.

Roentgenographic examination reveals widening and irregular fuzziness of the sacroiliac joints. Areas of localized absorption of bone occur nearby, or "spotty" atrophy of the adjacent portion of the sacrum is present. The cartilage is absorbed, and ankylosis of the bone takes place. The supporting ligaments become calcified, but the calcification does not spread. Roentgen therapy brings about some beneficial results. In the author's case the improvement was consistent over a period of four years. The total amount of radiation was 1,000 r divided into sixteen doses, given twice a week, and 1,000 r distributed over a large body area.

It is possible that the roentgen rays had their action on the mast cells, since it has been demonstrated experimentally that such rays affect the sulfuric acid excretion of these cells, and chondroitin sulfuric acid is found in the cartilage, tendons, ligaments and aorta. It is the author's conclusion (1) that the pathologic change in spondylitis adolescens is caused by absorption of cartilage, (2) that roentgen therapy benefits the disease by liberating sulfur within the body and (3) that in spondylitis adolescens chondroitin sulfuric acid is absorbed from the cartilage, ligaments and bone around the sacroiliac joints and spine and that this occurs because of a deficiency of sulfur or of mucoitin or chondroitin sulfuric acid elsewhere in the body.

GOTTEN, Memphis, Tenn. [ARCH. NEUROL. & PSYCHIAT.]

A CASE OF CONGENITAL OSTEOPSATHYROSIS WITH THE GENEALOGICAL TREE OF THE FAMILY. F. AUSTIN HENLEY, Brit. M. J. **1**:326 (March 7) 1942.

Henley reports a case of congenital osteopsathyrosis in a 47 year old man admitted to the hospital with a complaint suggestive of biliary colic. Because of blue scleras and other conditions which were not consistent with biliary colic, an investigation of his family history was made, which revealed a long line of relatives who had suffered from multiple fractures. The article contains the complete genealogic table, showing the high percentage of relatives with the same disease. In this record it was noted that all patients with blue scleras had sustained fractures. The most common age for fractures was in the preschool years. This condition appears to be transmitted through both males and females, provided that 1 of the parents possesses the characteristics. It was noticed that children who were normal at birth did not acquire the condition and did not transmit the disease. It is stated that the cause of the blueness of the sclera is its thinness; one sclera examined by Parsons was only one-third the usual thickness.

BIRDSONG, University, Va.

Diseases of the Eye

THE AETIOLOGY OF PHLYCTENULAR OPHTHALMIA. A. SORSBY, Brit. J. Ophth. **26**:159 (April) 1942.

This is the Hunterian Lecture of 1942.

The article begins with a review of the literature of phlyctenular ophthalmia. Statistical studies show that there has been a consistent decline in the number of cases of this disease in the United States and in several European countries. There are two exceptions: The data of the Hôtel Dieu, at Paris, disclose a practical continuous increase in the number of cases in the period 1912 to 1932, and the more important exception there was a consistently higher incidence reported in several centers during the first World War and its aftermath.

Phlyctenulosis is essentially a disease affecting children and young adults. Females are much more frequently affected than males. An increase in incidence in the spring has been noted by a number of observers.

Phlyctenulosis in tropical countries appears to have clinical and possibly also histologic features that differ from those seen in Europe and in the United States.

Among the attributed causes of the disease are nutritional deficiencies, focal infections, pediculosis capitis, endocrine disturbances and tuberculosis. Sorsby states: "Almost every possible fault in diet has been incriminated as the cause of phlyctenular ophthalmia. . . . Enlarged and septic tonsils are regarded by some observers as causal factors. . . . A growing volume of elaborate evidence is available on the significance of tuberculosis as the cause of phlyctenular ophthalmia. So far as the tubercle bacillus has not been found in phlyctenulae, and in that the implantation of the organism in the conjunctiva produces a tuberculous reaction and not a phlycten, the evidence is negative, but a mass of observations is available implicating tuberculous infection rather than tuberculous disease. . . . Since the introduction of the von Pirquet test in 1907 and its subsequent modification, a high percentage of positive tuberculin reactions has been consistently reported by a number of observers."

S. H. MCKEE and W. ZENTMAYER. [ARCH. OPHTH.]

THE AETIOLOGY OF PHLYCTENULAR OPHTHALMIA. A. SORSBY, Brit. J. Ophth. **26**:189 (May) 1942.

In his continuation of the article which appeared in the April issue, Sorsby analyzes the cases of phlyctenular ophthalmia observed at the White Oak Hospital, London. During the sixteen years from 1925 to 1940, 1,392 children with this disease were admitted to the hospital. The records of those treated between June 1935 and December 1940 were investigated. The following summary by the author covers the interesting points disclosed:

"It is concluded that phlyctenular ophthalmia is a manifestation, not of tuberculous disease, but of tuberculous infection, the phlycten making its appearance only when a hyperallergic phase is present and there is a suitable (? specific) exciting factor of endogenous or exogenous origin. It is suggested that the age distribution, sex-incidence and seasonal variation seen in phlyctenulosis are best explained on the assumption that the affection is tuberculous in character. The prognostic significance of the phlycten is graver than that of a positive tuberculin reaction in a child; this is borne out by the subsequent incidence of tuberculosis and mortality from it in children previously affected with phlyctenulosis." W. ZENTMAYER. [ARCH. OPHTH.]

Skin Diseases; Allergy

THE EFFECT OF WIDE VARIATIONS IN POTASSIUM AND SODIUM INTAKE IN ASTHMATIC CHILDREN. GEORGE F. HARSH and PAUL B. DONOVAN, J. Allergy **13**:105 (Jan.) 1942.

Harsh and Donovan summarize their study thus:

"1. The effect of wide variation in total ingestion of potassium and sodium on the symptoms of twelve asthmatic children has been observed under conditions that permitted the control or evaluation of such complicating factors as variations in diet, meteorologic conditions, and amount of air-borne allergens.

"2. There is some indication that a high-sodium intake increased the amount of asthma of the group, but a high-potassium intake had little or no effect." HOYER, Cincinnati.

THE RELATIONSHIP OF MATERNAL DIET TO INTRAUTERINE SENSITIZATION. BENJAMIN ZOHN. J. Allergy **13**:153 (Jan.) 1942.

A group of 21 mothers who had unusual cravings for specific foods during pregnancy were studied. Ten mothers has a history of allergy, and 11 did not.

Intracutaneous tests with the foods taken in excess were done on each infant on the second and eighth days post partum. Passive transfer tests with the cord blood were done in 14 of the 21 cases. No positive reactions were obtained in the children by either the direct or the indirect method of testing.

The foods taken in excess were chocolate, milk, eggs, strawberries, potatoes, buckwheat, bananas, plums and peaches.

HOYER, Cincinnati.

PROPHYLACTIC ORAL THERAPY AGAINST POISON IVY. HERMAN GOLD and PETER MASUCCI, J. Allergy **13**:157 (Jan.) 1942.

Twenty susceptible subjects were given tablets which contained the oleoresin of poison ivy. Seventeen of the group were considered to have been protected by the administration of the oleoresin.

HOYER, Cincinnati.

THE PRACTICAL MANAGEMENT OF ECZEMA IN INFANTS AND CHILDREN. EARL D. OSBORNE, JAMES W. JORDON and JOSEPH J. HALLETT, New York State J. Med. **42**:47 (Jan. 1) 1942.

Scratch, intradermal and patch tests are of very limited value in the management of eczema. "Actual clinical treatment is the only sure test." Investigation of definite reactions to various foods, contact substances, soaps, medicated oils, laundry chemicals, powders, wool, silk, feathers, dogs, cats, insect sprays, kapok, the mother's and father's cosmetic, hand lotions and toys should be made.

Dietary measures are of secondary importance, and not more than 10 to 15 per cent of cases of eczema are due to diet. A washed, distilled crude coal tar put up in a vanishing cream containing 10 per cent of zinc oxide is favored for local treatment.

AIKMAN, Rochester, N. Y.

OBSERVATIONS ON THE TREATMENT OF SCABIES. R. M. GORDON and D. R. SEATON, Brit. M. J. **1**:685 (June 6) 1942.

The fact that there are many treatments for scabies contradicts the old saying that "a disease with many remedies has no cure." However, because of the search for a better remedy there are numerous treatments for scabies, all of which have their advantages and disadvantages. The choice of vehicles for applying the sarcopticidal drugs is a rather important point. Certain of the soaps that are used for a vehicle are irritating to the skin, and mixtures such as paraffin and petrolatum have little penetrating power. It has been shown that animal and vegetable oils penetrate the skin well, and the authors have shown that tetraethylthiuram monosulfide, dimethylthianthrene and benzyl benzoate when mixed with equal parts of vegetable oil penetrate the skin rapidly and to an equal and similar depth. It is recommended by most dermatologists that before application of any drug the body should be thoroughly scrubbed with hot water and soap. This has been shown not only to make the skin more penetrable to the drug but to remove mechanically numerous superficial mites and eggs. It has also been found that patients with scabies treated under proper supervision in a hospital or under the discipline of the armed services get well much better than those treated at home.

It is also found that the necessity of disinfecting clothes is not as great as has been previously thought. However, because occasionally a patient is infected from old bedclothes or old clothes it is recommended that clothes be treated by the usual methods of disinfection.

An experiment was made on albino rats naturally infected with mites of the genus Notoedres. Three drugs, dimethylthianthrene, benzyl benzoate and tetraethylthiuram monosulfide, were applied in 50 per cent dilution in the methyl ester of the fatty acids of coconut oil. Before use they were saturated with scarlet red so that their subsequent distribution in the tissues might be determined microscopically. After the drug was massaged into the skin for three minutes, portions of the skin were removed twenty-four hours and three days later and examined microscopically. A single application of any of the drugs produced degenerative changes in almost all the mites within three days, but a small proportion of the eggs still remained unaffected. It was therefore suggested that a second application of the drug should be made after an interval of a week, by which time any egg which survived the first application would have hatched. Although no significant difference was detected between the actions of the three drugs, tetraethylthiuram monosulfide was more rapid and more lethal in its action than either of the other drugs used. Its superiority was such that it is worthy of a trial in human scabies.

BIRDSONG, University, Va.

Surgery and Orthopedics

PRE-OPERATIVE SEDATION IN CHILDREN. K. BORTHWICK-LESLIE, Canad. M. A. J. **46**:345 (April) 1942.

The metabolic rate is normally highest at 6 years; then it falls slightly until 10 years, rises during puberty and slowly declines to old age. Reflex activity and metabolic rate are parallel.

Even without considering the influence of outside factors it can be seen that a child will tolerate a larger amount of anesthetics and drugs per pound of body weight between 6 and 14 years than at any other period of its life. Fear, excitement, sleeplessness, elevated temperature and abnormal endocrine activity increase the requirement of anesthetic. In order to overcome these factors the author advises the giving of soluble pentobarbital U. S. P. or other barbiturate on the evening preceding the operation and forty-five minutes preoperatively. The advantages are that fear is lessened, the amount of anesthetic required is reduced by one fourth to one third, there is less vomiting and the postoperative amnesia and rest are valuable. The disadvantages are that increased postoperative nursing care is necessary and that it is difficult for the anesthetist to estimate the stages of anesthesia because of changes in the eyes in the reflexes.

MOORE, Omaha.

Miscellaneous

A STUDY OF ANTIDOTES FOR FLUORINE. S. MARCOVITCH and W. W. STANLEY, J. Pharmacol. & Exper. Therap. **74**:235 (Feb.) 1942.

Sodium fluoride is commonly used as a roach powder, and through its being mistaken for baking powder and other substances deaths have occurred. Studies were made on roaches, rats and rabbits to find an antidote for this poison. Rats fed small amounts of sodium fluoride gradually lost weight and died in about a month. Aluminum sulfate given together with the fluoride considerably lessened the toxicity of the fluoride. Other salts were less effective than the aluminum salt. Given by mouth with the fluoride to rabbits, 2 parts of the aluminum sulfate neutralized 1 part of the fluoride; however, such mixtures were much less effective in killing roaches. As large doses of the fluoride kill animals in one to three hours, there is still need for an effective antidote that is effective some time after the fluoride has been taken.

PILCHER, Cleveland.

OBSTETRIC PROBLEMS ARISING FROM EXCESSIVE SIZE OF THE INFANT. KARL M. WILSON, New York State J. Med. **42**:883 (May 1) 1942.

Wilson presents a report of a study of a series of 495 infants weighing 4,000 Gm. or over at birth. The gross fetal mortality was 4.8 per cent and increased progressively with the weight of the child. It was 100 per cent in 3 infants weighing over 5,500 Gm. The greatest difficulty was due to shoulder dystocia. Birth injuries such as Erb's palsy and fractured clavicles also occurred. There was no maternal mortality. Two children who weighed 6,000 Gm. were born dead. The largest living child delivered by cesarean section weighed 5,410 Gm.

AIKMAN, Rochester, N. Y.

A TENTATIVE TEST FOR PYROGEN IN INFUSION FLUIDS. CO TUI and M. H. SCHRIFT, Proc. Soc. Exper. Biol. & Med. **49**:320 (March) 1942.

The authors have used rabbits for preliminary tests and dogs for confirmatory tests in determining the presence of pyrogens in various solutions. If in trained rabbits given 50 cc. per kilogram of body weight of various solutions at the rate of 10 cc. per minute, a rise of 5 degrees C. developed in one to three hours, a presumptive evidence of the presence of pyrogen was obtained. If in dogs given 250 to 1,500 cc. of fluid intravenously at the rate of 30 cc. per minute, a rise in temperature of 0.5 degree C. and leukopenia developed in one to three hours, this indicated the presence of pyrogen. This twofold test was done 214 times with 172 negative results, and this corresponded with the clinical results. The 42 positive results also were confirmed by clinical data. These tests can be depended on to detect the presence of pyrogen sufficient to cause moderate reactions in patients.

HANSEN, Minneapolis.

THE SHORTCOMINGS OF HUMAN HEAT REGULATION IN COLD WEATHER. OTTO KESTNER, Brit. J. Phys. Med. **5**:33 (Feb.) 1942.

The "ice reaction" affords a helpful indication in picking out children who would benefit by being sent to a sheltered place. A simple test was used to determine this reaction.

Three ice cubes were applied to the chest and the time for producing (*a*) faint redness and (*b*) definite red coloration was determined by a stopwatch. With hardened patients faint redness appeared immediately and more pronounced redness in five to fourteen seconds. With delicate children hardly any red reaction appeared even after thirty-three to sixty seconds. The children in the latter group were said to have a negative reaction and were introduced gradually to the open air.

HARTMAN, Cleveland.

PHYSICAL MEDICINE: A REVIEW AND A POLICY. MORTON SMART, Brit. J. Phys. Med. **5**:60 (April) 1942.

This is the leading article in this issue of the journal. The author believes that physicians in general are skeptical about the usefulness of physical medicine because of a lack of knowledge concerning the whole field. Both patients and physicians often confuse the well trained physical therapeutist with a practitioner of one of the many cults. Physical therapy is frequently believed to be some form of new system for recognizing and treating disease.

Physical medicine should be considered as an integral part of the practice of medicine and should not occupy a subordinate place among hospital services. The present war and industrial activities offer a great opportunity for physical medicine to demonstrate its value, and the author suggests the immediate establishment of an institute of physical medicine. The objectives of such an institution are outlined.

HARTMAN, Portsmouth, Va.

IS LEAD POISONING COMMON IN CHILDREN? K. N. BAGCHI, Indian J. Pediat. **9**:69 (April) 1942.

Lead poisoning may result from inhalation even more rapidly than by ingestion. A frequent source in Bengal is a cheap substitute for vermillion that contains red lead which is used as a cosmetic preparation in the hair or on the forehead. The children of women using this substance are exposed to fairly high concentrations of lead and may show intoxication. The symptoms are indefinite, such as marasmus, convulsions, anemia and enteritis, and may be present only after some other febrile illness.

TENNEY, Madison, Wis.

MICROBIOLOGIC BASIS OF SULFANILAMIDE THERAPY. JULIUS HIRSCH, Compt. rend. Soc. turq. d. Sc. phys. et nat. **10**:1 (Feb. 6) 1942.

The oxygen consumption of "resting" (not multiplying) bacteria is not influenced by the addition of sulfathiazole or other derivatives of sulfanilamide. Under corresponding experimental conditions, other disinfecting materials, such as rivanol and mercury bichloride, produce an instantaneous decline in the oxygen consumption of the bacteria.

Sulfonamide compounds have no bactericidal action in vitro. In a suitable medium the addition of sulfathiazole depresses the speed of multiplication of the bacteria at a rate which corresponds to the concentration of the drug. Sulfathiazole and other derivatives of sulfanilamide have about the same depressing action as a graduated reduction of the temperature. The depression of the speed of multiplication is the *only* effect of the drugs; bacteriostasis is their *maximal* antibacterial effect.

The sulfonamide compounds do not become active before the multiplication of the bacteria has taken place for a certain period of time. The larger the number of bacteria, the less pronounced is the effect of the sulfanilamides.

Vegetable and animal products such as peptones and extracts from yeast, from bacteria and from bran contain two types of substances: "inhibitors," which depress the action of the sulfonamide compounds, and "accelerators," which speed up the multiplication of bacteria in synthetic mediums. The author succeeded in separating both factors in yeast extract by precipitation with mercury acetate. The "accelerators" are found in the precipitate; the filtrate contains the "inhibitors."

One mol of paraaminobenzoic acid is capable of inactivating 1,000 mols of sulfanilic acid, 100 mols of sulfanilamide and 1 mol of sulfathiazole.

The author discusses the possibility that paraaminobenzoic acid is present in bacterial, in vegetable and in animal protein, and that it participates in synthesizing the bacterial plasma.

ARON, Chicago.

Society Transactions

CHICAGO PEDIATRIC SOCIETY AND CHICAGO HEART ASSOCIATION

JESSE R. GERSTLEY, M.D., *President, in the Chair*

Joint Meeting, April 20, 1943

Exercise for the Child with Rheumatic Heart Disease. DR. GEORGE EISENBERG.

The child with rheumatic heart disease whose infection is quiescent is usually limited in exercise to an unnecessary degree. This unwarranted caution undoubtedly stems from proved therapy for active rheumatic infection in children. But after recovery from active infection, a large group of children with normal-sized or moderately enlarged hearts and with mitral or mitral and aortic regurgitation are never permitted to experience the degree of activity which they might reasonably undertake without harm.

The material for this paper was collected from yearly reports of observations on children with cardiac disease at Sunset Camp. These cover a period of twenty years. Sound evidence has been accumulated that activities of most of the children with such disease have been too sharply limited.

It is more logical to allow the child with inactive rheumatic heart disease to determine, within reasonable limits, his tolerance for exercise than to impose strict limitations on his activities. Each child seeks or reaches that level of play which is comfortable and gratifying. The real danger to the child with this condition of the heart is recurrent infection and not play or exercise.

DISCUSSION

DR. ROBERT A. BLACK: I think there is a great deal of merit in many things Dr. Eisenberg brought out. All who handle these rheumatic children realize that the great difficulty is to decide when rheumatism is really arrested. When my associates and I first began our work at LaRabida Sanitarium we were astonished at the gains in weight and had to lower the caloric diet to avoid the problem of overweight. We now allow the convalescing children more freedom than when we started. However, I think still that rest is the important factor when the children are in a rheumatic phase. Every one here has seen exercise increase the extent of the infection if the rheumatism is not in the quiescent stage. The amount of exercise such children can stand is almost unlimited when they are adequately compensated and well over the infectious process.

How long does it take to recover from the infectious process? We started at the sanitarium with an average stay of two and a half months by each patient. We had so many returned to us with symptoms of relapse that we began increasing the period to three and a half months. Again they were sent back to us, and now we keep them from five to six months. It is rather difficult to say why these children are forced to come back. Our routine is explained to the parents when they take the children home. The relapse may be due to overexercise or lack of uniform temperature, with subsequent colds resulting in reactivation of the rheumatic virus. It makes me wonder if the benefit these children derive from our care does not revolve around the fact that we have them under strict observation and care when a simple infection of the respiratory tract occurs. I think that in the arrested stage of rheumatism they should be permitted gradually to increase their exercise. I stress definitely the difference between competitive work and play and normal work and play.

Of most of such patients in my private practice what Dr. Eisenberg has said is true, for these children are under supervision in the home. I cannot see that many of these little patients are handicapped by being kept from too little exercise. I would say that they should be given all the exercise they are capable of having. I do not think many are kept unusually quiet, for in my opinion it is not possible to keep a well child quiet.

DR. ROBERT S. HERZOG: This presentation commendably stresses the fact that in the past there has been too much overconservation about the activity of these patients. There has been too much insistence on sitting around doing nothing for six months or a year, or, indeed, on confinement to bed, for children who were able to go to school or to be working. But I should not like to see the pendulum swing too far in the opposite direction. One should not

condone chronic or acute severe fatigue. After all, whatever is good hygienic procedure for a normal child or adolescent is no less so for a patient with heart disease. There is often a tendency to overlook that. The physician should be specific not merely about the kind of exercise or play but about its duration in minutes or hours, the hours a day allotted to exercise and play and the length of the rest period. Progressive graduation of exercise is not unimportant.

My associates and I are not in a position to say that exercise may be unlimited as long as rheumatic infection is inactive. In that third of the instances of recurrent infection not preceded by an infection of the upper respiratory tract, how does one know just what may or may not have been predisposing? Important as the recurrent infection is in initiation of congestive heart failure, one may not forget the instances of mechanical failure or of failure without active myocarditis. I have 2 patients with these conditions under care now and, further, have made pathologic studies on others. These two were unreasonably overactive, and failure chiefly of the right side of the heart developed with no clinical evidence of infection. Neither followed the recommended regimen (which included attendance at school); in both the condition should have been preventable. One had had no active infection for about seven years and still has none. If exercise is not too important, one might ask why hearts with congenital infections fail.

Does Dr. Eisenberg have any objective data from his experience at the camp to coorelate with his impressions and procedures, which have been so timely and so well presented?

Dr. Stanley Gibson: Dr. Eisenberg's paper deserves a wide hearing. For many years the child with rheumatic heart disease has been arbitrarily restricted. If one can be sure that the patient is free from active infection, there is, so far as I have been able to learn, no reason why he should not be allowed to exercise freely, provided he stops short of actual fatigue. Children are willing to cooperate under these circumstances, whereas if they are constantly nagged they develop a rebellious, unhappy attitude and, in addition, usually contrive to do exactly what has been forbidden to them.

Dr. Isaac A. Abt: This has been a stimulating discussion on physical exercise for patients with heart disease. Each new generation rediscovers medical methods and practices that were employed in a previous generation but have been abandoned or forgotten. In the nineteenth century Theodore Schott and his brother August combined gymnastic exercises with carbon dioxide baths at Nauheim for the treatment of patients with chronic heart diseases. Exercises for increasing resistance were given slowly and carefully under control of the pulse rate; these physicians thought that gentle exercise dilated blood vessels and that this was a beneficial reaction. The Schott brothers attracted patients to Nauheim from all over the world for the baths and the resistance exercises. Max Joseph Oertel, of Dillingen, Bavaria, advised his patients to eat high protein foods with reduction of liquids and to climb hills. Oertel thought that the regimen and the exercise which he advised tended to diminish the accumulation of water in the body, strengthened the heart muscle, caused reduction of body weight and thus prevented obesity.

It goes without saying that exercise should be permitted only to those children who are afebrile and whose hearts are fully compensated. There is another point for physicians to consider in allowing gymnastic exercises for patients with heart disease; I think it is preferable to individualize rather than to generalize the amount of exercise permitted. Some will take it well; others will become fatigued and show cyanosis and dyspnea if the exertion has been excessive. Such patients should be under critical observation.

Hypertrophy of the heart may occur if exercise is overdone; excessive hypertrophy may be disastrous. Well controlled exercise for a child recovered from an acute cardiac disturbance is an advantage. I know several boys who insist on indulging actively in all the sports, such as swimming, baseball, football and running. It can be stated conservatively that the boy who is doing all these things is not living safely within his limited cardiac reserve.

Dr. Jesse R. Gerstley: Dr. Eisenberg suggested that an adolescent or juvenile patient with heart disease will select the proper amount of exercise as a baby will select a proper diet from a tray. This may be true in camps for persons with heart infections, where such children are trained. But what can one say about letting a child crippled with heart disease run and play with normal children, who will exercise until exhausted? Is it not likely that the injured child will be stimulated to play beyond his endurance?

Dr. Clifford G. Grulee: I recall 2 patients whom I have followed for more than twenty-five years. In both instances I have felt that the course of the condition has justified my dependence on the judgment of the children as to how much effort they could use at a given time; this is in support of the experience of Dr. Eisenberg.

LIEUTENANT COMMANDER JAMES H. WALLACE: I should like to ask Dr. Eisenberg to express his opinion on a clinical question which arises when one follows these children through adolescence and their early twenties. Are there possible factors in growth and adolescence which have something to do with their tolerance for exercise? Many rheumatic children go through a stormy period between the ages of 5 and 14 years and then make an astonishing improvement at the advent of puberty, going through adolescence remarkably well. A little later, in their early twenties, they begin to show a little dyspnea on mild exertion and other evidence that their hearts are not so competent. What causes the improvement in tolerance for exercise during adolescence, and is the evidence of beginning incompetence of the heart in early adult life due to reactivation of infection or to a mechanical factor?

DR. GEORGE EISENBERG: Dr. Herzog asked if there were any specific data which would help confirm our impression as to the safety of exercise for children with heart disease without active infection. In recent years we have carried out two experiments, one on tolerance for exercise. This one was begun by Dr. James Wallace and was repeated every few years by some physician at the camp. The best thing to be said about tests of exercise tolerance is that they do not differentiate between children with heart disease and normal children. The last one was made with the use of the basal metabolism test, oxygen consumption being measured after a certain amount of exercise. The only children who showed impaired cardiac tolerance were several with cyanosis from congenital heart disease. The point of tolerance must be greatly extended to obtain positive results. We did not have any children with cardiac failure, but apparently positive results are also obtained in such children.

Of interest also were roentgen studies (the other experiment), showing no correlation between tolerance for exercise and size of the heart. The children with mitral and aortic disease, having fairly large hearts, may have good tolerance for exercise; a child with a normal-sized heart may be mentioned as having fair tolerance. This also was confirmed by Wilson, who said there was no relation between tolerance for exercise and size of the heart.

In reply to Dr. Wallace, at camp we did observe that children past adolescence and children who came back for a number of years seemed to have better tolerance for exercise than younger children.

Dr. Herzog asked about congestive heart failure without infection and said he had observed 2 instances of it. I do not believe existence of such a condition is possible. I think children who have congestive heart failure have had active rheumatic infection, and this has been shown at autopsy.

Dr. Gerstley asked whether children would overexercise. I do not believe that a child who exercises vigorously can be hurt. He will be tired, but after adequate rest will be all right, as would a normal child. He must be treated like a child who is normal.

Dr. Black asked how one can be sure of the presence of active infection. This is determined clinically and by laboratory tests, such as determination of the sedimentation rate and the blood count. Dr. Herzog performed 2,000 sedimentation tests at Sunset Camp, and one of his conclusions was that in every case of active infection the sedimentation rate was high.

Education must be directed away from telling the children what they cannot do and toward telling the parents that the child may have an active infection and that in such a case he should be taken to the physician at once.

Complete Heart Block After Diphtheria: Report of a Case. DR. ROWINE M. HAYES.

Myocardial damage is a common and severe complication of diphtheria. It may consist of injury to the myocardium or to the mechanism of conduction. Changes in conduction, especially auriculoventricular and intraventricular block, are serious, and patients in whom complete heart block develops almost invariably die within a short time after onset of the block.

We have at present a patient who became ill with a severe attack of diphtheria of the "bull neck" variety on Nov. 21, 1942. He received 60,000 units of diphtheria antitoxin on the fourth day of illness. His pulse rate, which had ranged between 100 and 132, dropped, until on the eleventh day it reached 46 and 38. This was accompanied by abdominal pain, vomiting, hepatomegaly and albuminuria. A diagnosis of myocarditis was made. He was treated by intravenous injection of hypertonic solution of dextrose. He made a gradual recovery and was discharged on his thirtieth day in the hospital.

Four days later he was admitted to Children's Memorial Hospital with a postdiphtheritic paralysis involving the lips, palate and extremities. His pulse varied between 70 and 90. An electrocardiographic tracing revealed a complete heart block with an auricular rate of 120 and a ventricular rate of 90.

Rest in bed was maintained. He made a complete recovery from his postdiphtheritic paralysis, but has had a persistence of his complete heart block until the present time, five months after the onset of diphtheria and four months after his first electrocardiogram was made.

The history of this child is unusual in that he recovered from a serious attack of diphtheria complicated by heart block, that he had a complete block in the presence of a normal pulse rate and that he has a persistent complete heart block at present, although he appears to be entirely well. A thorough search of the literature reveals only 2 or 3 instances of permanent heart block which may have been caused by diphtheria

DISCUSSION

DR. STANLEY GIBSON: The course of the disease in this patient violates all the rules set down for cases of diphtheritic myocarditis. Complete heart block having developed, the patient should not have survived. In the few instances in which survival has occurred, the block has usually disappeared within a short time. This has not happened in the present case. I am still puzzled as to whether the cardiac rhythm may yet return to normal and whether this child's activity should be restricted still for fear of a sudden catastrophe.

DR. SIDNEY STRAUSS: Use of the electrocardiograph is the easy way to make a diagnosis of heart block. Since the auricular rate is so near the ventricular rate, it is difficult but may be possible for one to see the extra-auricular beats in the veins of the neck. Then there is the sharp accentuation of the first sound when the auricular and ventricular beats come together; that would make one suspect a heart block. I admit that use of the electrocardiogram is easier.

Heart block per se does not give disability. People may live for years with this condition and get along satisfactorily. The questions here are: How much damage has occurred? What caused the injury to the bundle of His and its branches? What is the damage in other parts of the heart? If the bundle of His has entirely healed and the rest of the heart is not much involved, I venture to say that this child will get along well.

DR. WILLIAM A. BRAMS: I think an understanding of the physiology of complete heart block would help a great deal in determination of the cardiac deficiency and the prognosis. Ordinarily, the pulse rate is slow (from 35 to 40). This may be explained as follows: As a result of the slow rate there is greater time for diastole, which means more time for the heart to fill and stronger cardiac output. The systolic pressure is high for this reason, and the diastolic is low, because there is a longer time for the peripheral vessels to empty and thus to produce a large pulse pressure. Obviously the real efficiency of the heart depends on the ventricular rate and myocardial capacity. If the rate is in the seventies or the eighties, the patient's condition is not much worse. If, however, the time comes when the ventricular rate slows down, the patient will have difficulty, especially on exertion, when he needs a greater supply of peripheral blood and cannot get it by increased heart rate. Also, as Dr. Strauss mentioned, an important factor is the condition of the myocardium.

As to the permanency of damage in this case it is difficult to offer any statement. I do not think that the specific conducting tissue regenerates. The recovery that sometimes occurs is due to release of pressure on this tissue by resorption of adjacent inflammatory exudate or gumma. When that is relieved the block decreases, as can be demonstrated experimentally. One good thing is that, since this patient already has complete heart block, he will not get an Adams-Stokes syndrome.

Traumatic Cardiac Injury in a Child. DR. EDWIN D. BAYRD and DR. STANLEY GIBSON.

R. V., a Negro boy 11 years of age, while coasting on his sled, was hit by an automobile. He lost consciousness for a short time. On admission to the hospital, he complained of a headache and severe pain in the left side of the upper part of his abdomen. Physical examination revealed a tense abdomen and a loud, harsh systolic murmur and thrill over the precordium. He had been seen many times previously in the outpatient department, and his heart was consistently noted to be normal. The electrocardiogram was not remarkable. He was discharged from the hospital at the end of a week. Ten days later he returned to the outpatient department, at which time it was discovered that the cardiac murmur was now musical, completely different from the harsh, rumbling murmur previously heard. The thrill persisted. An electrocardiogram revealed an elevated ST segment in lead IV and deeply inverted T waves in leads II, III and IV. Subsequent electrocardiograms showed the progressive changes which are found in patients with coronary occlusion. He was kept in bed for six weeks. During this period he had no complaints except of a "sticking" pain over his heart in the early part of his course. He has since returned to school.

The electrocardiograms offer proof that he suffered myocardial damage. The location, timing and quality of the murmur lead us, from our own experience and from reports in the literature, to believe that he suffered a rupture of the interventricular septum. The change in the character of the murmur which was noted about seventeen days after the accident might be explained in a variety of ways. The defect may have narrowed or enlarged, or the chordae tendineae or the papillary muscle may have ruptured. This case is unique. We have found no similar case in medical literature.

Acute Bacterial Endocarditis in Presence of Patent Ductus Arteriosus: Apparent Cure of Patient Following Ligation of Ductus. DR. RALPH B. BETTMAN.

DISCUSSION

DR. W. A. BRAMS: I saw this patient before operation and can confirm what Dr. Bettman has said; I understand that she has served as a blood donor since the operation. This matter of operating on a patent ductus arteriosus brings up a question with which we were never faced before. Should it be operated on only when it is infected with bacterial endarteritis, or should it be done prophylactically? According to Maud Abbott's statistics, more than 22 per cent of patients with bacterial endarteritis died, which is a large percentage of deaths to be caused by a supposedly harmless congenital defect.

There is a shunt of blood into the pulmonary artery, and evidence shows that on an average about 50 per cent of the output of the left ventricle is turned back into the pulmonary artery and then into the lungs and the left side of the heart. This blood cannot enter the right side of the heart because of the pulmonic valves. This means that in order for it to flow from the heart into the peripheral arterial system the left ventricle has to work with about 50 per cent more effort than in a normal heart. In the few cases I have observed all patients have shown preponderance of the left side of the heart in the electrocardiogram. There is a question whether the operation should not be done as a prophylactic measure because of the great incidence of infection and because of the mechanical strain. The congenital defect is borne well, both by the child and by the adult. Another patient, a woman aged 32 years, who had patent ductus arteriosus received surgical treatment. This patient had a history of rheumatic fever at the age of 20 years. She was thin, weighing about 80 pounds (36 Kg.), and complained of weakness, palpitation and some cardiac symptoms. There was no other defect. In view of what Dr. Bettman told us, I decided that she should have an operation. It is still a question as to whether this should have been done, since she had a history of one attack of rheumatic fever. I should like to have the pediatricians answer this.

DR. GEORGE EISENBERG: I think one must keep in mind the great variation in types of patent ductus conditions patients in a clinic for children's heart diseases have. My associates and I see a large percentage of children who seem to be free of symptoms and rarely see a child with patent ductus in whom bacterial endocarditis develops. It might be better for such children not to undergo the operation, inasmuch as the risks involved make the outcome questionable. On the other hand, we have seen recently a child with patent ductus arteriosus with a pulse resembling that of marked aortic regurgitation, an extremely large heart and difficulty in carrying out normal routine. Certainly surgical treatment might be considered for such a child—especially for one in whom subacute bacterial endocarditis finally develops.

DR. RALPH B. BETTMAN: The finding of a negative blood culture seems to be the experience of many writers. Certainly it occurs as soon as the operation is performed. I know of other instances in which the blood culture was negative within a day's time.

As to whether patients with simple patent ductus arteriosus but without a Streptococcus viridans infection should be operated on, I agree with Toroff, in spite of the fact that we had a hemorrhage during this surgical treatment. The patient was extremely emaciated, and probably there was some disturbance around the area in which we were working. Thinking that the heavy ligatures I applied in the first operation would not be necessary, I used a fine silk suture. This cut into the ductus as I tied a knot, and a hemorrhage resulted. I feel that the operation will be done more easily and with less mortality if it is performed before the development of any inflammatory reaction at the site of the ductus. Dr. Brams and I had several long discussions prior to operation in the last case, and I think that if we had another such case we should both recommend operation. There is no question any more that in every case of a patent ductus arteriosus with a superimposed Str. viridans infection there should be surgical treatment as soon as the condition has been diagnosed.

Book Reviews

Autonomic Regulations. By Ernst Gellhorn, M.D., Ph.D., Professor of Physiology, College of Medicine, University of Illinois. Price $5.50. Pp. 373, with 80 illustrations. New York: Interscience Publishers, Inc., 1943.

This is an excellent book which has grown out of lecture notes in course work given over the last nine years at the University of Illinois School of Medicine. It is a summary of extensive research work in this field by Dr. Gellhorn and his associates for the past decade.

The book is organized into five sections: (1) a brief introduction to the anatomic and physiologic foundations of the autonomic nervous system; (2) a section showing the role of the autonomic system in adjustment reactions of the organism involving primarily the respiratory and circulating systems; (3) a useful and instructive section on autonomic-endocrine integration; (4) an exposition of autonomic-somatic integration, and (5) a section on results and applications dealing with a very extensive analysis of some principles of autonomic organization and adjustment reactions in physiologic and pathologic conditions, as well as in general and spinal anesthesia, and finally a chapter on the autonomic nervous system and neuropsychiatry.

There is a rather extensive bibliography of some 1,100 references, though all the papers in this field are not included. Each of the nineteen chapters has a convenient summary, and there is an excellent system of cross references throughout the book. Most of the illustrations are from the work of Gellhorn's laboratory, many of them previously unpublished.

This work emphasizes the presentation of the material from an organismic point of view with an attempt to integrate the various facts and principles into an organic whole. This approach is very useful, and the book should be a help to practitioners, teachers and students. The book brings up to date the knowledge of many of the important reaction systems of the body and stresses the important role of both the sympathetic and the parasympathetic system in many bodily adjustments tending to maintain homeostatic conditions.

The book is clearly written, and most of the arguments are well documented, with a sufficient indication of the experimental work on which they are based to allow a critical reader to evaluate the point of view presented by the author. There are some instances, however, in which general statements seem to go beyond conclusions which would be justified by the data given. For example, on page 168 the author makes the following statement: "Fig. 45 shows how, under the influence of 6.2 percent oxygen, respiration increases and the blood pressure rises, although at the same time the linguo-maxillary reflex is abolished. Since the centers involved in the linguo-maxillary reflex and in the control of blood pressure and respiration are all in the brain stem, it is hard to conceive that the inhibitory influence of higher centers may be different on various brain stem centers." The graph referred to by the author shows that there is first a period of augmentation of the linguomaxillary reflex before its depression, a fact entirely neglected by the author, and, furthermore, there is no record at all of respiration or circulation on the graph. The concept of differential action by higher centers on lower regions of the central nervous system is certainly well established, despite the apparent assumption by the author to the contrary in this instance.

The author makes such a sharp distinction between anoxia and hypercapnia that one is likely to overlook the fact that in most asphyxial conditions both are present and that anoxia is seldom unaccompanied by at least some change in the carbon dioxide content of the tissues and blood.

Gellhorn's theory that schizophrenia is essentially due to a relative preponderance of the vagoinsulin system over the sympatheticoadrenal system and that the basis of many alleged cures of the condition lies in the stimulation of the latter system needs more substantiation than is offered by the facts presented before it can be fully accepted. On the whole, however, this book represents a valuable contribution to physiologic literature and thought and should be welcomed by most biologists and physicians.

Clinical Significance of the Blood in Tuberculosis. By Gulli Lindh Muller, M.D. Price, $3.50. Pp. 536, with 52 tables. New York: The Commonwealth Fund, 1943.

This book deals chiefly with the hematologic findings in pulmonary tuberculosis of the reinfection type in different stages of development. It is based on a comprehensive analytic survey of pertinent literature as well as on a total of 6,819 complete blood examinations, which included red and white cell counts and corrected sedimentation rates, performed under standardized conditions on 1,000 consecutive patients. The correlation between variations in the hematologic picture and various manifestations of the disease in different stages of development is ably discussed in detail.

In six separate parts of the book the following topics are given very thorough consideration: (1) the physiology of the blood-forming organs and the cellular response to the tubercle bacillus; (2) the changes in circulating blood cells in tuberculosis; (3) the sedimentation rate; (4) clinical and hematologic data as measures of constitutional reaction; (5) the effect of therapy, exercise and complications on the hematologic picture, and (6) examinations of the blood applicable to tuberculosis.

The author has succeeded admirably in meeting the present need for a modern interpretation of the clinical significance of the hematologic findings in tuberculosis. The features of Dr. Muller's book that make it particularly valuable include the bibliography of 604 references, the discussion and interpretation of the literature, the tables showing the clinical and numerous hematologic studies made on 1,000 patients in the three stages of pulmonary tuberculosis and the analysis of these studies. Physicians interested in tuberculosis will welcome this publication.

The Inner Ear. By Drs. Joseph Fischer and Louis E. Wolfson. Price, $5.75. Pp. 421, with 77 illustrations. New York: Grune & Stratton, 1943.

If one is looking for a complete presentation of the functions and derangements of the internal ear in a few easy pages, this is not it! If one wishes to dig out by rather heavy reading the known facts concerning this most interesting organ from a well digested mass of experiment and observation and controversy, this book will prove valuable. The reader will realize how complex the subject is and will be baffled by the wide divergence of experimental results and conclusions. For the otologist it contains much valuable information and concisely reviews most of the important work that has been done; it will enable him to work toward a full understanding of the vestibular and cochlear functions. For other physicians, unless they are especially interested in this subject, it is likely to prove confusing and will not offer too much that is clinically applicable. The confusion is due not to the authors' presentation but to a subject itself which has not yet been clarified down to its fundamentals.

The Neuromuscular Maturation of the Human Infant. By Myrtle B. McGraw. Price, $2.00. Pp. XIV + 140, with 28 illustrations. New York: Columbia University Press, 1943.

This excellent volume brings up to date the recorded information on the correlation between behavior and the development of the nervous system and includes the results of valuable research work of the author. The behavior of an infant depends on the maturation of his central nervous system and not on his training program.

There is a description of the developmental anatomy of the nervous system of infants, neonatal behavior, development of the neuromotor activities, early sensory development and individual development and a final chapter on maturation and learning.

This small volume should prove reassuring, interesting and instructive to every one having anything to do with children.

Los derivados sulfonamidicos en el tratamiento de las diarreas infantiles. By Francisco J. Menchaca. Paper. Price, not given. Pp. 130. Buenos Aires: El Ateneo, 1943.

Sulfanilamide, sulfapyridine, sulfathiazole, sulfadiazine, sulfaguanidine and succinylsulfathiazole are each considered under the headings of experimental study, absorption, effect on diarrheal disturbances, dosage and toxicity. The last part of the book is given to reports of cases from the author's experience in which each of the drugs was used. This monograph is well written and well organized. There is a full bibliography of the Spanish and foreign literature on the subject.

News and Comment

GENERAL NEWS

American Board of Pediatrics, Inc.—The following examinations are scheduled for the spring of 1944: Written examinations will be held locally, under a monitor, on Feb. 4, 1944, and oral examinations will be held in Philadelphia, on March 25 and 26, and in San Francisco, on May 6 and 7, 1944.

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